CT 22/82/01

NCI/ICRDB/CT22 82/01

PB82-939601

ICRDB CANCERGRAM

MELANOMA AND OTHER SKIN CANCER

Diagnosis, Treatment

SERIES CT22 No. 82/01

JANUARY, 1982

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DIAGNOSIS

1. BODY COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF MALIGNANT MELANOMA METASTASIS.

Bydder GM, Kreel L
Div. Radiology, Newham District, Queen Mary's Hosp. East End, West Ham Lane, London E15, England

CT; 5(1):21-24 1981

Experience with body computed tomography (CT) in 32 patients (10 male, 22 female; mean age of 49.7 yr) malignant melanoma metastases is described. Positive findings were recorded on 27 CT examinations, although this included one case (presacral kidney) were the incidental finding was the only positive finding. Other incidental findings included gallstones, intrathoracic goiter, multicystic ovaries, and emphysema. Lymph node involvement was the most common finding and the pelvis was the most common metastatic site. Clinically suspected metastases were confirmed on 19 examinations (50%). These involved the lung (2 cases), liver (1), axillary lymph nodes (3), mediastinum (2), abdomen (1), and pelvis (9). Local re currences were confirmed in two cases. Clinically suspected

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metastases were not confirmed in five cases. Additional metastases were diagnosed in 14 cases. One additional metastasis was identified. Additional lymphadenopathy was demonstrated in the mediastinum in three cases, but this finding was more common in the abdomen (5 cases) and pelvis (4 cases). Although local recurrences were suspected on clinical grounds, CT was useful in demonstrating the extent of the disease. No definite evidence of bony metastases was seen. Although the adrenal glands were marginally enlarged in two cases, these findings were regarded as equivocal. The usefulness of CT in the diagnosis of metastases of malignant melanoma is discussed. (9 Refs)

2. OCCURRENCE OF UVEAL MALIGNANT MELANOMAS IN EYES WITH CONGENITAL MELANOSIS OCULI (MEETING ABSTRACT).

Ferry AP
Medical College of Virginia, Richmond, VA, 23298
International Symposium on Intraocular Tumors, May 17-20, 1981, Schwerin, W Germany European Ophthalmology Society: :A15 1981

Congenital melanosis oculi (CMO) is an uncommon, usually unilateral, hyperpigmentation of the uveal tract, episclera, sclera, and optic nerve. Uveal malignant melanomas are believed by some authors to occur more often in eyes with CMO than in normally pigmented eyes. A minority view is that the incidence of uveal melanoma is no greater in patients with CMO than it is in patients with normally pigmented eyes. In a consecutive series of 100 enucleated eyes containing malignant melanomas of the choroid or ciliary body, the majority of which I had examined clinically, four eyes had CMO. Thus, in the population of 100 eyes with posterior uveal melanomas, four per cent had CMO. The incidence of CMO in the general population, although unknown, is certainly far less than four per cent. These data support, therefore, the contention that people with CMO are more likely than are normally pigmented persons to develop uveal malignant melanomas, although the risk is undoubtedly far less than the often quoted 25 per cent figure. The true incidence with which uveal melanomas develop in patients with congenital melanosis oculi remains to be determined. This will require a long term clinical study, rather than being based solely on review of material in a pathology laboratory. (no Refs)

3. PRIMARY CUTANEOUS MELANOMA AND SMALL CONGENITAL NEVOCELLULAR NEVI: HISTOLOGIC ASSOCIATION AND ESTIMATION OF RISK (MEETING ABSTRACT).

Rhodes JH, Day CL, Sober AJ, Harrist TJ, Mihm MC, Fitzpatrick TB
Department of Dermatology, Harvard Medical School, Boston, MA
J Invest Dermatol; 76(4):319 1981

We searched for a nevocellular nevus (NCN) in the histologic specimens of 234 primary cutaneous melanomas (all histologic types and invasive at least to Level II) occurring in postpubertal Caucasians. All cases interpreted as having an associated NCN required unanimous acceptance of at least the dermal component of a NCN by four of 4 reviewers. A NCN was designated congenital if it had one or more 'specific' histologic findings. A NCN was associated with melanoma in 57 cases (24.4%) and was less likely to be found when tumor thickness was greater than 4.5 mm versus (vs) less than or equal to 4.5 mm. Of the 57 cases having a NCN, 16 had 'congenital' features acccunting for 6.8% of all melanoma cases. None of the 234 cases was associated with a giant NCN. Assuming that the prevalence of small congenital NCN is identical in Caucasian adults and newborns, we estimate for the small congenital NCN a relative risk of 8.7. We estimate for an adult that the 'chance' association of a small congenital NCN and melanoma within the same area must occur with a frequency less than 1/10,000. On the basis of an observed association of 6.8%, which is markedly higher than the expected, and an almost 9-fold increase in estimated risk of melanoma associated with a small congenital NCN, we strongly support that consideration be given to routine prophylactic excision of small cogenital nevocellular nevi. (2 Refs)

4. FACTORS RELATED TO THICKNESS OF MELANOMA: MULTIFACTORIAL ANALYSIS OF VARIABLES CORRELATED WITH THICKNESS OF SUPERFICIAL SPREADING MALIGNANT MELANOMA IN MAN.

Kopf AW, Rigel D, Bart RS, Mintzis MM, Hennessey P, Karris MN, Ragaz A, Trau H, Friedman RJ, Esrig B
Skin and Cancer Unit, 562 First Ave., New York, NY, 10016
J Dermatol Surg Oncol; 7(8):645-650 1981

A series of 18 variables in cases of malignant melanomas was examined in order to identify those that correlate with thickness of primary cutaneous malignant melanoma of the superficial spreading type. A multifactorial analysis was then performed on those variables that correlated with thickness in order to determine their order of dominance. Information on 820 patients was used for this study. Of the variables tested, 12 showed, in descending order, statistically significant correlations with thickness: Clark level, elevation of the lesion, age of the patient, least diameter of lesions, history of bleeding, history of ulceration, stage, largest diameter of lesion, location, pedunculation, stage at entry into the study, and satellitosis. Factors not correlated with thickness included regional lymphadenopathy, in-transit metastases, duration of the lesion, sex, history of a previous malignant melanoma, and history of a preceding lesion at the primary site. The stepwise multiple regression analysis performed on the 12 variables that correlated with thickness revealed that the most influential factors with respect to thickness were Clark level, elevation, greatest diameter, ulceration, stage, and age of the patient. These results and those published from similar studies are discussed. (26 Refs)

5. SERUM CERULOPLASMIN LEVELS IN SURGICAL CANCER PATIENTS: RELATIONSHIP WITH TUMOR STAGE AND POSTOPERATIVE COMPLICATIONS (MEETING ABSTRACT).

Dionigi P, Dionigi R, Pavesi F, Mazari S, Goggi D
Istituto di Patologia Chirurgica, Universita di Pavia, I-27100 Pavia, Italy
Eur Surg Res; 13(1):31 1981

The concentration of serum ceruloplasmin (CP) is known to increase in a variety of acute and chronic conditions including solid tumors, Hodgkin's disease, and leukemias. Moreover, it has been shown that a preoperative increase of CP levels could be predictive for higher susceptibility to sepsis. The mechanism which determines these variations is not completely known. CP has been evaluated at admission in 109 surgical cancer patients (48 males, 61 females, mean age 57 yr) divided in 5 groups: breast (29), *melanoma* (10), lymphoma (12), esophagus-stomach (35), sigma-rectum (23); 33 controls (27 males, 6 females, mean age 41 yr) were normal subjects or patients with minor surgical benign lesions. Tumor stage (I-IV) was evaluated following UICC classification. Patients were defined septic if they presented after surgery a diagnosed focus of infection or if they had an undiagnosed fever for at least 3 days. CP has been evaluated by single radial immunodiffusion technique. Cancer patients presented significantly higher values of CP than controls. Minor differences were observed in melanoma, whereas CP was more significantly increased, esophagus-stomach, sigma-rectum and lymphoma. CP did not correlate with sex and age within the 5 groups considered; on the contrary a positive correlation was found with tumor stage. In fact, the lower levels of CP were observed in patients at stage I, intermediate values at stage II and III and higher values at stage IV. Elevated values of CP were observed at admission more frequently in cancer patients who developed postoperative infections than in nonseptic patients. Nevertheless, the difference between mean values in these two groups was not statistically significant. The results of this study show a positive relationship between CP and tumor progression suggesting that variations of CP may have an important clinical value for the evaluation of the diffusion of different neoplasias. (3 Refs)

6. DERMATOPATHIC LYMPHADENOPATHY: COMPARISON OF CASES ASSOCIATED AND UNASSOCIATED WITH MYCOSIS FUNGOIDES.

Burke JS, Colby TV
Dept. Pathology, Stanford Univ. Medical Center, Stanford, CA, 94305
Am J Surg Pathol; 5(4):343-352 1981

Thirty-three biopsies of dermatopathic lymphadenopathy derived from 32 patients (18 male, 14 female; 17-80 yr old, mean age of 42.5 yr), who were without evidence of mycosis fungoides (MF), were compared with those of 33 nodes derived from 29 patients (23 male, 6 female; 24-74 yr old, mean age of 53 yr) with MF. All biopsies demonstrated histologic features of dermatopathic lymphadenopathy, but the degree of paracortical expansion (dermatopathic change) varied from focal to massive enlargement with severe distortion of the normal lymph node architecture. The magnitude of lymph node adenopathy was significantly increased among the lymph nodes associated with MF, in contrast to those unassociated with MF. The number of reactive follicles also was statistically greater in the MF group; associated sinus hyperplasia was relatively equal. The only other significant difference between the two groups of dermatopathic nodes was in the number of small round lymphocytes; more of these lymphocytes were found among the lymph nodes biopsies from the patients without MF (p = 0.02). (31 Refs)

7. CLINICAL PATHOHISTOLOGICAL FINDINGS OF SKIN LESIONS INDUCED BY MALIGNANT LYMPHOMA (MEETING ABSTRACT).

Kaneko K, Tashiro M, Tokunaga M, Sato E
Dept. Dermatology, Sch. Medicine, Kagoshima Univ., Usuki-cho, Kagoshima Pref. 890, Japan
Nippon Hifuka Gakkai Zasshi; 91(3):258 1981

Of 80 patients (32 with mycosis fungoides, 46 with non-Hodgkin malignant lymphoma, 1 with Sezary syndrome, 1 with Hodgkin's disease) with invasion of heterotypic lymphocytes found by skin biopsy, lymph node biopsy was performed in 50. The nature and distribution of exanthema, from clinical findings; the pattern and depth of tumor cell infiltration, with or without epidermal invasion, and heterotypic skin cells, from skin biopsy findings; and the degree of tumor cell infiltration, from lymph node biopsy, were determined. The correlation between each of the above items and prognosis was determined. Prognostic factors could be divided into favorable and poor for each item, but by combining them, prognosis could be predicted to some degree at the first examination. The presence or absence of a lymph node lesion was especially important. The necessity of lymph node biopsy was confirmed. (no Refs) (In JPN)

8. PROLIFERATING TRICHILEMMAL CYST: A SIMULANT OF SQUAMOUS CELL CARCINOMA.

Brownstein MH, Arluk DJ
Lab Dermatopathology, 2 Jordan Drive, Great Neck, NY, 11021
Cancer; 48(5):1207-1214 1981

Comparison of 50 proliferating trichilemmal cysts with 50 'ordinary' trichilemmal cysts indicated that both types almost invariably occurred on the scalps of women, were diagnosed clinically as cysts, followed a benign course, and featured trichilemmal keratinization. A spectrum was observed from trichilemmal cyst with minimal hyperplasia, to full-blown proliferating trichilemmal cyst. Occasionally, patients had ordinary trichilemmal cysts on their scalps associated with a proliferating trichilemmal cyst. In addition to trichilemmal keratinization, which is characteristic of the follicular isthmus, proliferating trichilemmal cysts showed a wider range of differentiation, including features of the follicu lar infundibulum, the lower nonkeratinizing portion of the follicular outer root sheath, and sebaceous cells. Intense inflammatory infiltrate and cellular atypia, sometimes of significant proportions, were also seen in proliferating trichilemmal cysts. It is concluded that trauma and inflammation may induce a trichilemmal cyst to proliferate and show a broader spectrum of pilosebaceous differentiation and cellular atypia of pseudocarcinomatous proportions, while maintaining its benign biologic behavior. (Author abstract) (7 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

9. FIRST USE OF TENNESSEE ANTIGEN IN CERTAIN GASTROINTESTINAL TUMORS (PRELIMINARY RESULTS) (MEETING ABSTRACT).

De Angeli S, Corradi G, Pontiggia P, Vimercati A
Centro per lo Studio e la Lotta Contro i Tumori, Ospedale Reg. di Vicenza, Vicenza, Italy
Tumori; 67(2,SupplA):175 1981

Tennessee antigen is a glycoprotein isolated from colonic tumors by Potter and Jordan and characterized by chemical, physico-chemical, and immunologic properties different from carcinoembryonic antigen (CEA). It has been primarily utilized in the definition and evaluation of gastrointestinal tumors with a specificity close to 100 per cent. The authors undertook to determine blood levels of Tennessee antigen in several non-gastrointestinal tumors and to evaluate their relation to CEA. They examined 200 patients with *melanoma,* breast and lung cancer. The subsequent results permit them to state that Tennessee antigen, at least from a qualitative standpoint, seems to be more sensitive and selective than CEA, being positive in about 80 per cent of breast tumors and approx 75 per cent of *melanomas.* In lung tumors the percentage positive was almost identical. The authors are seeking further confirmation of the data obtained by expanding the experimentation although the technic seems economical and easy to carry out. (no Refs) (In ITA)

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10. ONCOFETAL ANTIGEN-I: DISTRIBUTION IN HUMAN TUMORS.

Rees WV, Irie RF, Morton DL
(c/o Irie) Div. Oncology, 54-140 CHS, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
JNCI; 67(3):557-562 1981

Oncofetal antigen-l (OFA-l) is a human tumor-associated fetal antigen that cross-reacts with fetal brain. The biological distribution of this antigen was studied in a variety of histologic types of human tumors and normal tissues. A total of 170 human tumors and 89 normal tissues obtained from biopsied and autopsied specimens were tested by immune adherence absorption assay. The antigen was most prevalent in *malignant melanomas* (82%); next in order of incidence were lung carcinomas (71%), sarcomas (61%), brain tumors (58%), and breast carcinomas (53%). However, OFA-l was found in only 15% of gastrointestinal tumors. The four hepatoma specimens tested were negative for OFA-l. OFA-l was also present in metastases and normal-appearing tissues of patients with OFA-l positive tumors but was not found in normal tissues from noncancer patients. These studies demonstrated that OFA-l is widely distributed among human tumors. It appears to be more prevalent in tumors of ectodermal and mesodermal origin. (Author abstract) (34 Refs)

11. RESPONSE OF CUTANEOUS T CELL LYMPHOMA TO THERAPY WITH HYBRIDOMA MONOCLONAL ANTIBODY.

Miller RA, Levy R
Div. Oncology, Stanford Univ. Medical Center, Stanford, CA, 94305
Lancet; 2(8240):226-230 1981

A murine hybridoma monoclonal anti-T-cell antibody was given to a patient with advanced cutaneous T cell lymphoma. The patient tolerated 17 treatment courses over 10 wk without symptoms of toxicity. Each treatment caused a reduction in circulating T cells which reached a stable level after 2 wk of therapy. Antigenic modulation was observed after each treatment but was fully reversed within 3 to 4 days; therefore the treatment was given twice weekly. Monoclonal antibody produced a striking clinical response in skin, lymph nodes, and blood but complete remission was not achieved. Since the remaining disease was antigen postive, failure to eradicate all tumor cells was not a result of immunoselection. At no time did the patient show an antimouse immune response. (Author abstract) (11 Refs)

12. CONTROLLED STUDY OF ADJUVANT THERAPY OF STAGE I MALIGNANT MELANOMA: SURGERY VS SURGERY PLUS PROLONGED IMMONOSTIMULATION WITH BCG (MEETING ABSTRACT).

Canaletti R, Nouvenne R, Marola G, Rossi G, Sturba F, Bachetti G, Piva G, Pezzarossa G, Moroni P, Bonsignori M
Centro Medico Oncologico, Ospedali Riuniti, Parma, Italy
Tumori; 67(2,SupplA):89 1981

Patients with melanoma of the limbs, head and neck were admitted to the study; Clark level between 3 and 5; absence of regional and/or distant lymph node metastases. Following wide excision of the lesion performed within 4 wk, the patients were randomized into 2 groups: a) immunostimulation with BCG, b) no treatment (controls). BCG treatment was continued for 2 yr, however it was interrupted when the disease recurred. From June, 1975, till April, 1980 (the study is still in progress), 67 patients were admitted to the study 66 of whom are evaluable, 32 in the control group and 54 in the experimental group. The actuarial curves for free interval reveal a higher recurrence rate in the control group than the experimental group (p, 0.07). The median disease-free interval, estimated from an actuarial curve projection is 95 wk in the control group and 326 in the experimental group (p, 0.004). It is concluded that the study demonstrates the usefulness of BCG stimulation in melanomas of the limbs, head and neck. (no Refs) (In ITA)

13. EFFECT OF INTERFERON IN THERAPY OF SKIN AND HEAD AND NECK TUMORS.

Padovan I, Brodarec I, Ikic D, Knezevic M, Soos E
(c/o Ikic) Inst. Immunology, Zagreb, Yugoslavia
J Cancer Res Clin Oncol; 100(3):295-310 1981

The use of human leukocyte interferon (HLI) for treatment of 30 patients (12 females, 18 males; aged 44-91 yr) with skin cancers (3 on cheek and chin, 5 on lower lip, 7 on nose, 4 on forehead, 3 on ear shell, 2 on skin of the neck) and tonsil cancer (3 cases), tongue cancer (1), and benign tumor (1), is reported. The duration of treatment was 1-6 mo and HLI was administered in the form of infiltration injections into the tumor or its immediate vicinity. During the first 7-19 days HLI was administered daily, thereafter it was given 2-3 x/wk. A single daily dose was 3 x 10(5) units of crude, unpurified HLI. Histologically, there were 13 cases of squamous cell carcinoma, 15 of basocellular carcinoma, one case of neurogenic sarcoma, and one of benign skin tumor. Clinical results were excellent in 10 patients, very good in 10, satisfactory in 5, hardly effective in 2, and not effective in 3. Immunological testing revealed excellent results in nine, very good results in three, satisfactory results in four, hardly effective results in two, no effect in three, and tests were not performed in nine. HLI reduced the biologic potential of the infiltrative tumor growth and caused solidification of the basic tissue and proliferation of connective tissue, thus obstructing infiltrative growth and the possibility of metastases. (20 Refs)

14. MODULATION OF LYMPHOCYTE ACTIVATION BY PLASMAPHERESIS IN ADVANCED MALIGNANT MELANOMA (MEETING ABSTRACT).

Salinas FA, Wee KH, Silver HK
No affiliation given
Immunobiol; 159(1/2):27 1981

These patients were subjected to serial plasmapheresis with pre- and post-treatment serum and lymphocytes evaluated by the following in vitro assays previously described by us: circulating immune complexes (CIC), anti-xenogeneic oncofetal antibody (anti-XOFA), total serum sialic acid (SA), and mixed lymphocyte reactivity (MLR). Each patient was followed for 4, 6, 7, 9, 12, 16 and 19 mo respectively. On one-way MLR stimulation with allogeneic cells, patient's lymphocytes tended to incorporate less thymidine than controls and this value remained depressed or further decreased after plasmapheresis for all 25 treatments in patients A, B, E, F, and G. The single evaluable pre and post MLR in patient C and the first MLR of patient D demonstrated increased thymidine incorporation following plasmapheresis. Conversely, autologous thymidine incorporation consistently increased in all patients, but not in patients C and D. Each plasmapheresis led to a measurable decrease in CIC, anti-XOFA and SA. CIC and anti-XOFA concentrations were independent and related to tumor burden as reflected by SA. A dynamic interaction of immune reactants was observed during 27 plasmapheresis treatments. Assuming that similar clearance rates for CIC, free antibody and unbound antigen were achieved upon plasmapheresis treatment, and that antigen concentration in these patients remained consistently in excess due to increased tumor burden, we observed that factors which reflected patient MLR capability included both pretreatment concentrations of CIC and free antibody. Patients A, C, D, E, and G reported symptomatic improvement following treatments in the absence of objective response in their advanced disease. In view of the relationship of tumor burden, CIC and anti-XOFA to effect of plasmapheresis on MLR, more timely treatment in patients with less extensive disease should be evaluated. (2 Refs)

CHEMOTHERAPY

15. PHASE II EVALUATION OF CHLOROZOTOCIN IN PATIENTS MALIGNANT MELANOMA.

Houghton AN, Camacho FJ, Gralla RJ, Wittes R
Dept. Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Treat Rep; 65(7/8):705-706 1981

Chlorozotocin (CZ) was evaluated in a phase II study in 19 patients (13 males, 6 females; 31-82 yr of age, av 52 yr) with histologically confirmed malignant melanoma. Initial total dose was 200 mg/square meter (m2) in those without and 175 mg/m2 in those with prior chemotherapy; those with a Karnofsky performance status below 70 received 150 mg/m2. The CZ was given by rapid iv infusion in equal doses over 5 consecutive days. Treatments were repeated every 6 wk if platelets returned to 100,000/ul and WBC to 3,500/ul. Only one minor response (tumor reduction less than 50%) occurred in a 49-yr-old male who had previously received dacarbazine. A 25% reduction was noted in the size of sc, lymph node and liver metastases; the response lasted 3 mo. The remaining 18 patients experienced progression. The major dose-limiting effect was myelosuppression which did not result in morbidity or mortality. CZ was well-tolerated; four patients had mild nausea and vomiting. No renal or hepatic toxicity occurred. It was concluded that CZ at the dose and schedule used is not effective as second-line chemotherapy in advanced malignant melanoma. (6 Refs)

RADIOTHERAPY

16. PROTON BEAM IRRADIATION: AN ALTERNATIVE TO ENUCLEATION FOR UVEAL MELANOMAS (MEETING ABSTRACT).

Gragoudas ES, Goitein M, Verhey L, Constable I, Munzenreider J, Urie M, Suit H, Koehler A
Massachusetts General Hospital, Harvard Medical School, Boston, MA
International Symposium on Intraocular Tumors, May 17-20, 1981, Schwerin, W Germany European Ophthalmology Society; :A25 1981

Fractionated proton beam irradiation was used in the treatment of 70 uveal melanomas from July 1975, to October 1980, at the Harvard Cyclotron. The treated tumors were 4 (6 percent) small size (10mm or less in largest diameter and 2mm or less in height), 30 (43 percent) medium size (larger in either diameter or height than the small melanomas and up to 15mm in diameter and 5mm in height), and 36 (51 percent) large size melanomas (larger than 15mm in diameter or more than 5mm in height). The follow-up period ranged from 1 mo to 5 1/2 yr with 18 patients followed for more than 2 yr and 35 for more than a yr. Tumor regression has been achieved in all eyes with a follow-up of more than 12 mo. One eye has been enucleated because of total retinal detachment. Two patients developed metastatic disease and died, and two others died from unrelated causes. Proton irradiation has definite advantages over previously used methods for the treatment of small lesions and can be used successfully for the treatment of medium size and some of the large size melanomas. In addition our results showed less mortality than these patients would have experienced had enucleation been their treatment. (no Refs)

17. BETA - IRRADIATION WITH RU-106/RH-106 APPLICATORS OF CHOROIDAL MELANOMAS: SIXTEEN YEARS EXPERIENCE (MEETING ABSTRACT).

Lommatzsch PK
Augenklinik des Stadtischen Klinikums Berlin Buch, Berlin, E. Germany
International Symposium on Intraocular Tumors, May 17-20, 1981, Schwerin, W Germany European Ophthalmology Society; :A41 1981

Between 1964 and 1980 more than 205 patients suffering from choroidal melanoma were treated with Ru-106/Rh-106 beta-ray applicators. The av follow-up period of all patients is 5.3 yr; 74 of them have been observed for more than 5 yr after irradiation. The dose was calculated such as to hit the tumor cells at the apex of the tumor with at least 10,000 rad. Therefore approx 100,000 rad had to be delivered at the scleral surface. The irradiation time ranged between 4 and 10 days. 132 patients could be cured, 36 had to be enucleated and 37 died (21 from proven metastases) during the follow-up period. Beta-ray applicators are an alternative to enucleation if the tumor is not more than 5 mm in height and if the ciliary body is not involved. In comparison with enucleation there seems to be no higher risk of later metastases. Some observations seem to indicate a better survival rate for those patients who had undergone beta-irradiation. (no Refs)

SURGERY

18. A PROGNOSTIC MODEL FOR CLINICAL STAGE I MELANOMA OF THE TRUNK; LOCATION NEAR THE MIDLINE IS NOT AN INDEPENDENT RISK FACTOR FOR RECURRENT DISEASE.

Day CL, Sober AJ, Kopf AW, Lew RA, Mihm MC, Wood WC, Roses DF, Golomb FM, Postel A, Hennessey P, Harris MN, Gorstein F, Gumport SL, Raker JW, Malt RA, Cosimi AB, Fitzpatrick TB
Department of Dermatology and Surgery, Massachusetts General Hospital, Fruit Street, Boston, MA, 02114
Am J Surg; 142(2):247-251 1981

The determination of prognostic risk factors of primary cutaneous malignant melanoma was based on the evaluation on 254 case studies. The tumors were located on the trunk and there was no clinical evidence of metastatic disease. The patients underwent surgery including wide excision of the tumor and, in some cases, elective regional node dissection. They were followed up for at least 5 yr at increasing intervals. Five clinical variables and ten histologic variables were tested. The overall 5-yr-disease-free survival of the 254 patients was 78%. None of 70 patients with a primary tumor thickness of 0.75 mm or less had a recurrence. In 92 patients with primary tumor thickness of 0.76-169 mm the 5-yr-disease-free rate was 91.5%. In 14 patients with primary tumor thickness of 5.5 mm or greater, the 5-yr disease-free rate was 10%. In the group of patients (78) in which the primary tumor was 1.70-5.59 mm thick the 5-yr disease-free rate vs 56%. The prognostic model for clinical Stage I melanoma of the trunk therefore included three main groups: (1) high risk: greater than 3.6 mm in thickness located on the upper trunk; (2) intermediate risk: greater than 3.6 mm in thickness located on the lower trunk, or less than or equal to 3.6 mm in thickness, and greater than 6 mitoses/square mm (mm2), or less than or equal to 3.6 mm in thickness located on the upper trunk with nearly absent lymphocyte response; and (3) low risk: less than or equal to 3.6mm in thickness with less than or equal to 6 mitoses/mm2 located on the lower trunk, or less than or equal to less than 3.6mm in thickness with less than or equal to 6 mitoses/mm2 located on the upper trunk with a moderate to marked lymphocyte response. (25 Refs)

OTHER THERAPEUTIC MODALITIES

19. FRACTIONATED RADIATION AND HYPERTHERMIA: EXPERIMENTAL AND CLINICAL STUDIES.

Overgaard J
Radiumstationen, Inst. Cancer Res., 44 Norrebrogade, DK-8000 Aarhus C., Denmark
Cancer; 48(5):1116-1123 1981

The effect of fractionated radiation and hyperthermia was experimentally studied in a C3H mammary carcinoma and its surrounding skin. Simultaneous radiation and heat (42.5 C -60 min) with one or five fractions gave thermal enhancement ratios (TER) of approx 2.5 in both tumor and surrounding skin, and no improved therapeutic effect was obtained. Five fractions of sequential treatment with heating 4 hr after radiation reduced the tumor TER to about 1.4, but when 72 were allowed between the fractions, no thermal enhancement of the skin was observed. Thus, an improved therapeutic ratio was observed. Clinically, the combined treatment was studied in 12 patients with 49 metastases from ***malignant melanoma*** treated with different schedules of radiation and hyperthermia (approx 43 C for 30 min). Simultaneous treatment with three fractions in 8 days gave TER values in the skin between 1.2-1.4, but a similar effect was found in the tumor. Three fractions of sequential treatment in 8 days did not produce any thermal enhancement of the skin response, but still presented an apparent gain of the tumor response, and so seemed to increase the therapeutic effect. Based on these findings, the strategy for further clinical use of combined hyperthermia and radiation is discussed. (Author abstract) (32 Refs)

20. SKIN CANCER IN PATIENTS WITH PSORIASIS TREATED WITH COAL TAR.

Pittelkow MR, Perry HO, Muller SA, Maughan WZ, O'Brien PC
Section Publications, Mayo Clinic, 200 First St. SW, Rochester, MN, 55905
Arch Dermatol; 117(8):465-468 1981

For many yr, crude coal tar has been used for the treatment of psoriasis. The possible carcinogenic effect of crude coal tar and UV radiation (Goeckerman regimen), considered individually or in combination, has been of some concern to physicians. A 25 yr follow-up study was completed on 280 patients with psoriasis who were hospitalized and treated with crude coal tar and UV radiation at the Mayo Clinic, Rochester, Minnesota during the yr 1950 through 1954. The results of this study suggest that the incidence of skin cancer is not appreciably increased above the expected incidence for the general population when patients are treated with coal tar ointments. It seems that the Goeckerman regimen (topical crude coal tar combined with UV radiation) can be used with minimal risk for skin cancer in the treatment of psoriasis. (Author abstract) (22 Refs)

CASE REPORTS

21. INITIAL EVENT IN MYCOSIS FUNGOIDES OF THE SKIN IS VIRAL INFECTION OF EPIDERMAL LANGERHANS CELLS.

MacKie RM
Dept. Dermatology, Anderson Coll. Building, 56 Dumbarton Road, Glasgow G11 6NU, Scotland
Lancet; 2(8241):283-285 1981

Malignant transformation of T lymphocytes has been proposed as the primary event in the development of cutaneous lymphoid infiltrates of the mycosis fungoides (MF) type. The alternative hypothesis of initial viral infection of the immunologically competent epidermal Langerhans cell leading to a defect in Langerhans cell/lymphocyte interaction and subsequent faulty lymphocyte recirculation is proposed. In only a proportion of these cases does a true T-cell lymphoma develop. (Author abstract) (23 Refs)

22. PUVA (PSORALEN AND ULTRAVIOLET A) AND SQUAMOUS CELL CARCINOMA IN PATIENTS WITH PSORIASIS (MEETING ABSTRACT).

Stern RS, Parrish JA, Bleich HL, Fitzpatrick TB
Harvard Medical School, Boston, MA
J Invest Dermatol; 76(4):311 1981

In the initial 2 yr, 30 patients with psoriasis exposed to PUVA developed cutaneous carcinoma. Now, after 4 yr of prospective study 73 of 1140 (6.5%) patients over age 30 have developed a total of 145 cutaneous carcinomas. Of these 73, 40 patients had a total of 96 squamous cell carcinomas (SCC). While the incidence of basal cell carcinoma (BCC) was only modestly elevated, the observed incidence of SCC was 9.1 x that expected based on age, sex, and geographically specific rates. While there was no apparent relation of the number of PUVA treatments and the risk of BCC, after 80 PUVA treatments the relative rate developing a SCC compared to a BCC was 5-fold greater. No dose dependent increase in the relative risk of SCC was noted in those patients who were not previously exposed to cutaneous carcinogens. Comparing SCC and BCC patients, patients with SCC were younger had more PUVA treatments prior to first tumor more had prior exposure to ionizing radiation (53% vs 44%), or prolonged exposure to tar and UVB light (69% vs 44%), and had more tumors. These data suggest that PUVA acts as a promotor of SCC in humans previously exposed to cutaneous carcinogens; an effect that increases with higher numbers of PUVA treatments. (no Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

23. A CASE-CONTROL STUDY OF THE POSSIBLE ASSOCIATION BETWEEN ORAL CONTRACEPTIVES AND MALIGNANT MELANOMA.

Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW, Vessey MP
Dept. Community Medicine and General Practice, Univ. Oxford, Oxford, England
Br J Cancer; 44(1):45-50 1981

In a case-control study, we investigated 169 women aged 15-49 yr with malignant melanoma brought to the attention of the Oxford and South Western cancer registries during the yr 1971-76, together with 507 matched controls. Data about medical, reproductive, drug and smoking histories were obtained both by reviewing general practitioner (GP) records and from the women themselves by postal questionnaires. There was no significant evidence of any overall increase in the risk of melanoma in oral contraceptive (OC) users (data from GP records ever use vs never use, relative risk (RR) 1.34, 95% confidence limits 0.92-1.96; corresponding data from postal questionnaires - RR 1.13, limits 0.73-1.75). However, although not significant, the risk estimated from data in the postal questionnaires was higher in women who had used OCs for 5 yr or more (use greater than or equal to 5 yr vs never use, RR 1.57, limits 0.83-3.03). Previously demonstrated risk factors for melanoma, such as fair skin, blonde or red hair and Celtic origin were found to be commoner in the cases than in the controls. Data from the Oxford/Family Planning Association contraceptive study were also examined. Unexpectedly there was a strong suggestion of a negative association between OC use and melanoma risk, but the analysis was based on only 12 women with the disease. (Author abstract) (19 Refs)

24. SMOKING AND THE DEVELOPMENT OF METASTASES FROM MALIGNANT MELANOMA.

Shaw HM, Milton GW
Melanoma Clinic, Sydney Hosp., Macquarie St., Sydney 2000, Australia
Int J Cancer; 28(2):153-156 1981

Investigations on 2,583 malignant melanoma patients indicated that in both men and women, although there did not appear to be a causal relationship between cigarette smoking and melanoma, smoking did facilitate the spread of metastases. Significantly more ex-smokers or smokers than life-long nonsmokers first presented for melanoma treated with established metastases. Also, in patients with localized disease, metastases appeared within 10 yr more often in ex-smokers than in life-long smokers. (Author abstract) (13 Refs)

SELECTED PRECLINICAL STUDIES

25. ANTITUMOR ACTIVITY OF TUFTSIN ON MURINE MELANOMA IN VIVO.

Noyes RD, Babcock GF, Nishioka K
(c/o Babock) Dept. Surgery/Surgical Res. Lab., Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer Treat Rep; 65(7/8):673-675 1981

The effect of tuftsin on malignant melanoma was studied in vivo using a murine model system. It was found that tuftsin was capable of significantly reducing the number of tumor colonies appearing in the lungs of mice following iv administration of tumor cells. Although only a limited number of concentrations of tuftsin were used in our preliminary studies, it appears that tuftsin possesses antitumor activity over a wide range of doses. (Author abstract) (21 Refs)

26. PHOTOCONJUGATION OF 8-METHOXPSORALEN (8-MOP) WITH PROTEINS OF HUMAN MELANOMA CELLS (MEETING ABSTRACT).

Borkovic S, Fukuyama K, Epstein WL

Department of Dermatology, University of California, San Francisco, CA

J Invest Dermatol; 76(4):326 1981

The aim of this study is to demonstrate conjugation of 8-MOP with proteins of melanoma cells in the presence of UVA irradiation and to characterize this interaction morphologically and chemically. Melanoma cell monolayers were treated with varying concentrations of 8-MOP and varying dosages of UVA; cells were washed and examined by fluorescence microscopy for the presence of in situ bound 8-MOP. An aliquot of the cells was hand homogenized in 0.25 M sucrose; nuclear, melanosomal, microsomal, and soluble fractions were obtained by differential centrifugation. Each fraction was dialyzed, lyophilized, and solubilized in 0.8 M urea and assayed by fluorescence spectrophotometry. Proteins of the soluble fraction were subjected to Sephadex G-100 gel filtration and assayed as above. Morphological examination of treated cells showed that photoconjugation of 8-MOP increased with the concentration of the drug and the dosage of UVA. 10(-5) M 8-MOP and 12 hr of UVA at 60 uW/cm 2 showed maximal photoconjugation without causing cytotoxicity. Chemical determinations of protein fractions revealed that photoconjugation of 8-MOP occurred in the soluble, melanosomal, and microsomal fractions but not in the nuclear fraction. Large numbers of protein peaks were detectable in the soluble fraction by gel filtration; 2 of which, corresponding to mol wt of approx 70,000 and 45,000 showed fluorescence. We conclude that 8-MOP photoconjugation to proteins can occur in the tissue cultured melanoma cell. This phenomenon may have a role in the photochemotherapy of pigmentary disorders. (1 Ref)

27. SYNTHESIS OF NEW POLYAMINE DERIVATIVES FOR CANCER CHEMOTHERAPEUTIC STUDIES.

Weinstock LT, Rost WJ, Cheng CC

(c/o Rost), Univ. Missouri - Kansas City, Kansas City, MO, 64110

J Pharm Sci; 70(8):956-959 1981

Selected homologs, analogs, and acylated derivates of spermine and spermidine, together with several heterocyclic and aromatic compounds containing a novoldiamine side chain, were prepared and evaluated biologically. Several compounds possessed activity against B-16 melanoma and human epidermoid carcinoma of the nasopharynx. (Author abstract) (39 Refs)

28. MECHANISM OF ESTROGEN'S ACTION ON HUMAN MELANOMA (MEETING ABSTRACT).

Schleicher RL, Chandhuri PK, Beattie CW
Department of Pharmacology, University of Illinois Medical Center, Chicago, IL, 60612
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

We determined whether the action of estrogen on human melanoma was receptor mediated by exposing estrogen (ER) and progesterone (PGR) receptor positive and negative cells to estrogen (E2), progesterone (P) and Nafoxidine in vitro and following transplantation into athymic mice. Human melanoma ER sediments at 8 and 4s or 4s alone in 10-30% low salt sucrose gradients and is specific for estrogens. The sex of the recipient of transplanted melanoma cells influenced tumor ER content. ER positive tumors had a higher ER content when carried in female mice, perhaps reflecting receptor induction by the higher levels of circulating E2 in female athymic mice. E2 also induced a dose related increase in tumor ER and nuclear receptor when measured by exchange assay ater E2 exposure to male and female athymic mice. There was no change in receptor affinity for E2 in any treated group. Injection of male and female athymic mice bearing ER and PGR positive melanoma with P (1 or 25 ug/mouse) reduced ER and nuclear E2 binding in male and female mice. Nafoxidine (50 ug/day; 20 days) reduced cytosol binding of ER positive tumors to nonmeasurable levels. Changes in ER in response to steroid manipulation were reflected by changes in cell proliferation. Exposure of ER positive cells in E2 in vitro produced an initial increase in cell growth which diminished with duration of exposure. This reduction in the initial stimulatory effect of E2 on cell growth may reflect a refractoriness to continued exposure to E2, or relative cell density during the period of E2 exposure, since the stimulatory effect on growth was greatest when cell density was low and replication most rapid. Cell growth was inhibited at concentrations greater than 10(-8) M of E2. Taken together, our observations suggest that a sub set of human melanoma has a cytosol receptor protein which binds estrogen specifically and with high affinity is translocated to the nucleus and mediates the cell's response to E2. (no Refs)

29. DIFFERENTIAL EFFECT OF INTERFERON ON THE EXPRESSION OF TUMOR-ASSOCIATED ANTIGENS AND HISTOCOMPATIBILITY ANTIGENS ON HUMAN MELANOMA CELLS: RELATIONSHIP TO SUSCEPTIBILITY TO IMMUNE LYSIS MEDIATED BY MONOCLONAL ANTIBODIES.

Imai K, Ng AK, Glassy MC, Ferrone F
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
J Immunol; 127(2):505-509 1981

Incubation of cultured human melanoma cells with human leukocyte interferon did not change the expression melanoma-associated antigens (MAA) recognized by monoclonal antibodies and of Ia-like antigens but significantly increased the expression of HLA-A,B antigens and Beta2-microglobulin (B2-u). The effect is dependent on the dose of interferon and on the incubation time. Interferon-treated melanoma cells showed an increased susceptibility to lysis mediated by monoclonal antibodies to HLA-A,B antigens and to human B2-u; on the other hand, interferon-treated melanoma cells did not change in their susceptibility to murine natural (NK) cell lysis and to immune lysis mediated by monoclonal antibodies to MAA and to Ia-like antigens, and they displayed a reduced susceptibility to human NK cell lysis. Therefore, the increased susceptibility of interferon-treated melanoma cells to lysis mediated by anti HLA-A,B and anti B2-u monoclonal antibodies is likely to reflect the increase in cell surface expression of the corresponding antigens. (Author abstract) (29 Refs)

30. COMMON NEUROECTODERMAL ANTIGENS ON HUMAN MELANOMA, NEUROBLASTOMA, RETINOBLASTOMA, GLIOBLASTOMA AND FETAL BRAIN REVEALED BY HYBRIDOMA ANTIBODIES RAISED AGAINST MELANOMA CELLS.

Liao SK, Clarke BJ, Kwong PC, Brickenden A, Gallie BL, Dent PB
McMaster Univ., Health Sciences Centre, 1200 Main St., West, Hamilton, Ontario, L8N 3Z5, Canada
Eur J Immunol; 11(6):450-454 1981

The hybridoma system has been utilized to produce antibodies to characterize the cell surface antigens on human melanoma cells. On initial screening, two antibodies derived by the fusion of mouse myeloma cells (SP2/O-Ag14) and splenocytes from a mouse immunized with a melanoma cell line (CaCl 78-1) showed cross-reactivity with 10 melanoma cell lines and did not react with any of 4 epithelial cancer lines, or 4 normal adult fibroblast lines. However, because of reactivity with two neuroblastoma cell lines, additional testing with other neuroectodermal derivatives was carried out and revealed a broad cross-reactivity among melanomas, neuroblastomas, retinoblastomas and glioblastomas and against antigens shared by fetal but not adult brain. Thus, these results indicate the existence of common neuroectodermal antigens on melanoma cells. Before melanoma specificity can be claimed for, an antibody reactivity with nonmelanoma cells bearing these neuroectodermal antigens should be excluded. (Author abstract) (21 Refs)

31. STRUCTURAL PROPERTIES AND TISSUE DISTRIBUTION OF THE ANTIGEN RECOGNIZED BY THE MONOCLONAL ANTIBODY 653.40S TO HUMAN MELANOMA CELLS.

Natali PG, Imai K, Wilson BS, Bigotti A, Cavaliere R, Pellegrino MA, Ferrone S
(c/o Ferrone) Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
JNCI; 67(3):591-601 1981

The hybridoma 653.40S, constructed with splenocytes from an inbred BALB/c mouse immunized with cultured human melanoma cells, secreted an antibody that had been shown to recognize an antigenic determinant restricted to human melanoma cell lines. The monoclonal antibody (MoAb) 653.40S showed immunoprecipitation of two glycopolypeptides synthesized by melanoma cells, one with the apparent mol wt of 280,000 and the other one with a mol wt larger than 500,000. These two glycopolypeptides were not bridged by disulfide bonds and were peripheral rather than integral to the plasma cell membrane. Comparison of the reactivity of cells of the melanocyte lineage with the MoAb 653.40S and with the MoAb Q5/13 to human Ia-like antigens showed that the former reacted with proliferating melanocytes and melanoma cells, whereas the latter reacted only with melanoma cells. The MoAb 653.40S did not react with a large variety of surgically removed normal and tumor tissues except for some instances of basal cell and squamous cell carcinomas. These results suggested that double staining of pigmented skin lesions with the MoAb 653.40S and with an MoAb to Ia-like antigens may help to solve controversial diagnosis of melanoma. Furthermore, the MoAb 653.40S may be useful for radioimaging and immunotherapy of melanoma. (Author abstract) (32 Refs)

32. SUBCLASS-RESTRICTED HUMAN IGG-ANTIBODIES INVOLVED IN ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY (ADCC) AND INDIRECT IMMUNOFLOURESCENCE (IF) (MEETING ABSTRACT).

Hadam MR, Standhammer R
Institute of Immunology, Munich, W. Germany
Immunobiol; 159(1/2):187 1981

Melanoma patients' sera were investigated for IgG antibodies against cultured human melanoma cells by IF and ADCC using purified human lymphocytes as effector cells. Emphasis was laid on the immunochemical characterization of the antibodies involved rather than on the definition of specificity. Double-IF using TRITC-labelled R-F(ab')(2)-anti-human IgG in combination with FITC-Protein A brought up a number of sera containing primarily antibodies of the IgG3 subclass. These sera were not reactive in ADCC. Sera with high reactivity in ADCC were rare; they could not be shown to contain significant amounts of antibodies reactive in IF. However, preparative gel chromatography of selected sera on Sephacryl S-3 00 demonstrated ADCC-activity confined to the 7s-IgG peak. Affinity chromatography of ADCC-inducing sera on protein A sepharose related all activity to the bound fraction, ie IgG1, 2, 4, (5/5). However, in 7/7 isolated IgG3 proteins from IF-positive sera no ADCC could be found, whereas those antibodies were still highly active in IF. Furthermore, no ADCC-activity could be induced by removal of aggregates via ultracentrifugation or by sensitization of target cells. From these data we conclude that human IgG3 when bound to tumor cell targets as detected by IF is unable to mediate ADCC with human lymphocytes as effectors cells. Apart from the IgG3 nature of the antibodies, distinct density requirements of the antigen or variations in lateral movement within the membrane may as well account for the lack of ADCC. For induction of ADCC we propose that only some human IgG subclasses, presumably solely IgG2, will produce ADCC with human lymphocytes. This IgG subclass is the only one for which induction of ADCC against nucleated targets has been described, although all four IgG subclasses have repeatedly been shown to be inhibitory when added to an ongoing ADCC reaction. This might be indicative of differing prerequisites for inhibition or triggering itself. Along with that hypothesis, ADCC could be interpreted as a sort of anti-polysaccharide response which is known to be restricted to the IgG2 subclass in man. Only the repetitive nature of the polysaccharide antigens may allow sufficient effectotarget-cell interaction needed for ADCC to occur. (no Refs)

33. STRUCTURAL CHARACTERIZATION OF HUMAN MELANOMA-ASSOCIATED ANTIGEN P97 WITH MONOCLONAL ANTIBODIES.

Brown JP, Nishiyama K, Hellstrom I, Hellstrom KE
Div. Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
J Immunol; 127(2):539-545 1981

Monoclonal antibodies were used to study p97, a human melanoma-associated antigen (MAA). Four hybridomas, designated 4.1, 96.5, 118.1, and 8.2, were obtained by fusing mouse myeloma cells with spleen cells from mice immunized with human melanoma cells. Antibodies 4.1 and 8.2 were IgG1; antibodies 96.5 and 118.1 were IgG2a. Sequential immunoprecipitation (IP) and sodium-dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) showed that all four antibodies recognized the same 97 kilodalton (kD) protein. Binding studies with 125I-labeled antibody showed that antibodies 4.1 and 96.5 bound the same epitope, p97a. Antibodies 118.1 and 8.2 defined epitopes p97b and p97c, respectively. Six monoclonal antibodies (M17, L1, L10, R10, I12, and K5) specific for gp95, a 95 kD melanoma cell surface glycoprotein were also tested. Sequential IP showed that these antibodies bound p97; p97 and gp95 are thus identical. Binding studies showed that antibody M17 bound epitope p97a, and antibodies L1, L10, and R19 bound epitope 97c. Antibodies I12 and K5 defined two other epitopes, p97d and p97e, respectively. SDS-PAGE under on reducing conditions indicated that p97 is monomeric, probably with intrachain disulfide bonds. Cell-surface labeling of sialic acid residues and neuraminidase digestion showed that p97 is a sialoglycoprotein. Digestion of p97 with papain or trypsin produced a stable 40 kD fragment, which expressed epitopes p97a, p97b, and p97c, but not p97d or p97e. (Author abstract) (35 Refs)

34. HORMONAL REGULATION OF EPIDERMAL TUMOR DEVELOPMENT.

Lupulescu A
Electron Microscopic Lab., Wayne State Univ., 323 Medical Res. Building, 550 East Canfield Road, Detroit, MI, 48201
J Invest Dermatol; 77(2):186-195 1981

The effects of hormones and hormone-like substances such as thyroxine, estradiol, hydrocortisone, calcitonin, prostaglandins (F2alpha, A2) or hormone deficiency (hypophysectomy, gonadectomy) on the development of carcinomas in mice and rats induced by 3-methylcholanthrene were investigated. Thyroxine, PGF2alpha, calcitonin, and estradiol markedly enhanced the development of squamous cell carcinomas and basal cell carcinomas; an inhibition occurred following hydrocortisone, hypophysectomy, and gonadectomy. DNA labeling using [3H]-thymidine and radioautography revealed that DNA synthesis in neoplastic cells is also markedly influenced by the same hormones. Tumor histology and ultrastructure are profoundly affected and an increase of epithelial pearls, hyperchromatic basophilic cells, tonofilaments, polyribosomes, and lysosomes is observed following thyroxine and PGF2alpha. An increase of keratinization and intramitochondrial granules occurred with estradiol and increased sclerosis followed calcitonin. A marked reduction of cell organelles occurred after hydrocortisone, hypophysectomy, and gonadectomy. Scanning electron microscopy shows salient changes in tumor cytoarchitecture and cell surfaces (blebs, ruffles). These findings demonstrate that hormones can change the development of carcinomas, DNA synthesis as well as their cellular differentiation and consequently may be important modulators of epidermal carcinogenesis. (Author abstract) (20 Refs)

35. MODULATION OF TERMINAL DIFFERENTIATION AND RESPONSES TO TUMOR PROMOTERS BY RETINOIDS IN MOUSE EPIDERMAL CELL CULTURES.

Yuspa SH, Lichti U, Ben T, Hennings H
In Vitro Pathogenesis Section, Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Ann NY Acad Sci; 359:260-273 1981

To evaluate the mechanism of tumor promotion in epidermis, the effect of retinoids on the induction of ornithine decarboxylase (ODC) was studied in cultured newborn mouse epidermal cells. Retinoids could delay and alter Ca++-induced terminal differentiation but could not prevent cell death. Retinoic acid (RA) was found to inhibit markedly ODC induction by tumor promoter 12,O-tetradecanoyl-phorbol-13-acetate (TPA). ODC induction by UV was less sensitive to RA. The degree of inhibition by RA after combined exposure to TPA and UV was similar to that after exposure to TPA alone. It was suggested that the unique inhibitory effect of RA on ODC induction by TPA and on tumor promotion results from membrane changes. (40 Refs)

36. RETINOIDS INHIBIT PROMOTER-DEPENDENT PRENEOPLASTIC PROGRESSION IN MOUSE EPIDERMAL CELL LINES.

Colburn NH, Ozanne S, Lichti U, Ben T, Yuspa SH, Wendel E, Jardini E, Abruzzo G
Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Ann NY Acad Sci; 359:251-259 1981

The mechanism of retinoid inhibition of promoter-dependent preneoplastic progression was studied in mouse epidermal JB6 cell line. Simultaneous exposure to retinoic acid (RA; 10(-8) to 10(-5) M) was found to reduce by 51-88% the yield of 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced colonies. RA was also found to inhibit the induction of anchorage independence by other promoters such as mezerein. Since the simultaneous exposure to RA reduced the mitogenic effect of TPA by approx 10%, the targets of retinoids in antagonizing late-stage promotion by TPA were not involved in the mitogenic response. It was suggested that retinoids prevent induction of ornithine decarboxylase activity. (19 Refs)

37. A SERUM-FREE MEDIUM FOR A431 HUMAN EPIDERMOID CARCINOMA CELLS; INHIBITION OF GROWTH IN CULTURE BY MOUSE EPIDERMAL GROWTH FACTOR (MEETING ABSTRACT).

Barnes D
Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA, 15260
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

We have developed a serum-free medium which supports A431 growth as well as serum containing medium (SCM). The basic nutrient medium (BNM) was a 1:1 mixture of Ham's F12 and Dulbecco-modified Eagle's medium containing 1.2g/1 NaHCO3 and 15 mM 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid. To BNM were added 4 factors stimulatory for A431 cell growth (BNM4F): 10 ug/ml insulin, 10 ug/ml transferrin, 5 ug/ml cold-insoluble globulin (CIg) and 0.5 mM ethanolamine. Preincubation of culture dishes with 5 ug/ml CIg or serum spreading factor could substitute for addition of CIg directly to medium in which cells were plated. Cells plated at a density of 2.5X10(3)/cm2 in BNM4F grew with a doubling time (TD) of 30 hr; cell number after 6 days was 85-100% of that in plates with SCM. A small, reproducible increase in cell number was seen if BNM4F was further supplemented with 2 ug/ml glycyl-histidyl-lysine; small, inconsistent increases were sometimes seen upon addition of 5 ng/ml parathyroid hormone or 100 ng/ml somatostatin. A431 cells also grew in BNM, but at a reduced rate. Addition of EGF at concentrations mitogenic for other cell types caused marked inhibition of A431 growth. Inclusion of EGF in the medium also reduced plating efficiency and prolonged the time lag before onset of growth after plating; cell number after 6 days in culture in BNM4F with 100 ng/ml EGF was about 10% of cell number in BNM4F. Inhibitory effects of EGF were detectable at 1 ng/ml in BNM4F and also were seen in BNM and SCM. Cells exposed to 10 ng/ml EGF in BNM4F for 72 hr and changed to BNM4F without EGF resumed growth with TD near that of unexposed cell after a lag of about 72 hr. Decrease in cell number due to inclusion of 10 ng/ml EGF in BNM4F could be prevented partially by the simultaneous addition of 2.5 ug/ml rabbit anti-EGF antibody. A431 cells produced tumors in athymic mice of either sex. (no Refs)

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FEBRUARY, 1982

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DIAGNOSIS

1. LYMPHOSCINTIGRAPHY IN MALIGNANT MELANOMA: 99MTC ANTIMONY SULFUR COLLOID.

Sullivan DC, Croker BP, Harris CC, Deery P, Seigler HF
(c/o Seigler) Dept. Surgery, Duke Univ. Medical Center, Durham, NC, 27710
AJR; 137(4):847-851 1981

Lymphoscintigrams were performed using technetium-99m antimony sulfur colloid in 21 patients with cutaneous malignant melanoma. Scintigraphic results were concordant with clinical prediction of lymph drainage in 6 of 11 patients with trunk melanoma, in 5 of 7 patients with extremity lesions, and in 0 of 3 patients with scalp melanoma. Thirteen patients showed ac-

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tivity in more than one regional node group. Eleven patients had focal activity in areas other than regional node groups (ie, in-transit or central lymph nodes). Lymphadenectomy was performed in 19 patients. In each case, the regional lymph node area chosen for resection was positive scintigraphically. The presence of 99mTc activity in excised lymph nodes was documented by scintillation counting and autoradiography. Metastatic disease was found in the resected nodes of 12 patients. Lymphoscintigraphy may be useful in planning lymphadenectomy in some patients with cutaneous melanoma. (Author abstract) (9 Refs)

2. STAGE I MELANOMA OF THE SKIN: EVALUATION OF PROGNOSIS ACCORDING TO HISTOLOGIC CHARACTERISTICS.

Van Der Esch EP, Cascinelli N, Preda F, Morabito A, Bufalino R
(c/o Cascinelli) W.H.O. Collaborating Centres on Melanoma, Instituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy
Cancer; 48(7):1668-1673 1981

The prognosis for Stage I melanoma of the skin was evaluated on the basis of histologic characteristics of 699 primary tumors collected by the WHO Melanoma Group from September 1967 to September 1975. Variables considered were max tumor thickness, levels of invasion, histologic type, number of mitoses, cell type, growth pattern, inflammatory reaction, angioinvasion and ulceration. When considered as single factors, these criteria, but cell type and inflammatory reaction, significantly affected survival (p less than 0.05). However, when each criterion was adjusted by max tumor thickness, the number of mitoses and ulceration only were found to be still significant. The type of cells, which is not significant by itself ($p = 0.92$), becomes significant ($p = 0.02$) when adjusted by max thickness. The most important prognostic factor was max tumor thickness ($p = 10(-9)$). Using this criterion this series was divided into three groups: (1) 'good prognosis' with max thickness not exceeding 2 mm and a 5-yr survival rate of over 80%; (2) 'intermediate prognosis' with max thickness between 2.01-4.00 mm and a 5-yr survival rate between 50 and 80%; (3) 'poor prognosis' with max thickness greater than 4.01 mm and 5-yr survival rate of under 50%. All other prognostic criteria were evaluated within each group and it was found that the 'intermediate prognosis' group cannot be divided into subgroups with different survival. The best survival was observed in patients with primary tumor not thicker than 2.00 mm with no ulceration ($p = 0.01$) or with spindle cells ($p = 0.03$); the worse survival was observed in patients with primary melanoma thicker than 4 with ulceration ($p = 0.04$) or with more than one mitosis per higher power field ($p = 0.04$). (Author abstract) (26 Refs)

3. STAGE I MALIGNANT MELANOMA OF THE SKIN: PROGNOSTIC VALUE OF THICKNESS AND LEVEL.

Palangie A, Lassau F, Moreau T, Noury-Duperrat G, Cottenot F
Service de Dermatologie, Hopital Saint-Louis, 2 place du Dr A. Fournier, F 75010 Paris, France
Nouv Presse Med; 10(28):2337-2341 1981

In a retrospective study of 95 patients seen between 1950 and 1978, the outcome of malignant melanoma levels III, IV and V of Clark's classification was reviewed. Patients with lentigo malignant melanoma were excluded. The overall survival rate was 63% at 5 yr and 48% at 10 yr. For the whole population of patients significant differences in survival rate were associated with level ($p = 0.00002$), thickness (less than 2 mm or greater than or equal to 2 mm; p less than 0.00001) and histological type ($p = 0.02$). The significance of prognostic variables taken separately was calculated by the Breslow method and was found to be $p = 0.0005$ for thickness, $p = 0.0009$ for patient's age and $p = 0.02$ for histological type. In analysis with two variables, including level, thickness was the variable that added most to the information on prognosis supplied by level. For the population of patients with melanoma levels III and IV significant differences in survival rate were associated with thickness (less than 2 mm or greater than or equal to 2 mm; p less than 0.001), though not with level. When the variables were studied separately, thickness and patient's age were significant ($p = 0.02$ and $p = 0.03$, respectively). Analysis with two variables, including thickness, showed that age was the variable that added most to the information on prognosis supplied by thickness. (Author abstract) (29 Refs) (In FRE)

4. ELECTRON MICROSCOPIC INVESTIGATION ON THE LOCAL CELLULAR REACTION TO PRIMARY MALIGNANT MELANOMA.

Szekeres L, Daroczy J
Dept. Dermatology, Medical Univ. Szeged, PO Box 480, Szeged H-6701, Hungary
Dermatologica; 163(2):137-144 1981

Five untreated primary malignant melanomas with relatively long duration have been investigated. Particular attention has been paid to the local cellular reaction observed in the intermediate zone lying between neoplastic and non-neoplastic tissue. Activated macrophages and histiocytes were seen as well as lymphocytes and lymphoid cells with cerebriform nuclei. Also, Langerhans cells were found in this zone and a close contact between these cells and melanophages was observed. The importance of the peritumoral cellular reaction in the local defense to neoplasma is discussed. (Author abstract) (21 Refs)

5. MALIGNANT LENTIGO-MELANOMA - A COMPARATIVE HISTOLOGICAL AND ELECTRON MICROSCOPY STUDY.

Bigotti A, De Martino C, Natali P, Sciarretta F, Colizza S
Laboratorio Patologia, Instituto Reginal Elena, 00100 Roma, Italy
J Surg Oncol; 18(1):31-37 1981

We examined, by light and electron microscopy, three cases of malignant lentigo, one of which was in the vertical growth phase. The purpose of our work was to compare the diverse patterns between superficial spreading melanoma and malignant lentigo. The observations suggest the following major findings: (1) the cells of malignant lentigo differ from normal melanocytes, and in the same specimen they differ from one another, (2) in malignant lentigo, melanosomes at Stage II-IV are visible; and (3) in spreading melanoma, the melanosomes do not attain complete maturation. These morphological features explain the different behavior of these two types of tumors. (Author abstract) (4 Refs)

6. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY QUANTITATION OF N-ACETYLNEURAMINIC ACID IN MALIGNANT MELANOMA AND BREAST CARCINOMA.

Silver HK, Karim KA, Gray MJ, Salinas FA
Cancer Control Agency British Columbia, 2656 Heather St., Vancer, B.C. V5Z 3J3, Canada
J Chromatogr; 224(3):381-388 1981

A rapid isocratic high-performance liquid chromatography (HPLC) method for quantitation of serum N-acetylneuraminic acid (NANA) is described. Separation is achieved on an Aminex HPX-87 cation-exchange resin using a 0.006 N sulfuric acid mobile phase. Compared with the more conventional thiobarbituric acid (TBA) method, HPLC is more reliable and has a much improved max sensitivity of 0.8 nmol/ml. In a limited study of malignant melanoma patients' sera, HPLC gave slightly higher values for NANA than TBA. In a more detailed study of breast carcinoma patients with measurable tumor burden, HPLC and TBA methods were used on the same sera and compared with concurrent carcinoembryonic antigen (CEA) determinations. HPLC resulted in a clear improvement in discrimination between tumor burden groups compared with either the TBA method or CEA. (Author abstract) (35 Refs)

7. KERATIN POLYPEPTIDE MODIFICATIONS INDUCED BY HUMAN PAPILLOMA VIRUSES (HPV).

Staquet MJ, Viac J, Thivolet J
(c/o Thivolet) ERA CNRS 788, Hopital Edouard Herriot, Laboratoire de Recherche Dermatologique et Immunologie, F-69374 Lyon Cedex 2, France
Arch Dermatol Res; 271(1):83-90 1981

Keratin polypeptide composition in different types of warts was studied. Superficial cornified scales of deep plantar, common, and flat warts, and whole lesions of condylomata acuminata were used for keratin protein extraction. Following extraction, proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Five main polypeptides [mol wt 67, 65, 63, 57, and 55 kilodalton (K)] and four minor bands were found in normal human plantar and dorsal skin; the quantity of 67K was lower in dorsum than in plantar extract. Similar results were obtained for warts, with an additional band of mol wt 72K. Distribution of polypeptides in the different types of warts is given. Marked decrease and even absence of 67 K in warts was the most significant feature. Viral infection seems to modify the distribution of proteins involved in the latest stages of keratinocyte differentiation. (30 Refs)

8. DETECTION IN CELLS OF HUMAN EPIDERMAL TUMORS OF CROSS-REACTIVE ANTIGEN COMMON FOR SQUAMOUS EPITHELIUM AND GROUP A STREPTOCOCCI.

Beletskaia LV, Barenbein BA, Silagadze DG, Kolesnikova VIu, Ezhov NIa, Kogan MG, Liampert IM
Lab. Streptococcal Infections, N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR
Biull Eksp Biol Med; 91(6):712-714 1981

Analysis of surgery specimens of skin basal cell and squamous cell carcinomas showed the presence of antigen cross-reacting with group polysaccharide of streptococci A. This tissue-specific basal cell antigen could not be detected in cells of entodermal tumors (stomach and intestinal adenocarcinoma). (12 Refs) (In RUS)

9. THE HYALINE ECCRINOMA.

Kwittken J
P.O. Box K, Tenafly, NJ, 07670
Mt Sinai J Med (NY); 48(5):426-430 1981

A histologic analysis of six so-called cylindromas has been performed. Results indicate origin from the secretory segment of the eccrine apparatus. Stromal proliferation about tumor lobules was a prominent feature in all cases. It is recommended that this lesion be termed hyaline eccrinoma. The myoepithelial cell might possibly prove to be the primary cell of origin of this tumor as well as the eccrine spiradenoma. (Author abstract) (6 Refs)

10. KAPOSI'S SARCOMA: CLINICAL FEATURES, EXPERIENCE IN UGANDA.

Kyalwazi SK
Dept. Surgery, Makerere Medical Sch., Kampala, Uganda
Antibiot Chemother; 29:59-67 1981

Kaposi's sarcoma (KS) typically begins in one of the lower limbs, usually the foot, with pitting edema and progresses to hard edema ('woody' edema). The disease may remain static in this form or may affect the opposite limb. In most cases the disease does not progress beyond this stage. In a few cases one of the upper limbs becomes involved, and within a short time the other limb develops the disease, and the tumor may spread to the trunk. KS apparently causes no disability beyond disfiguring appearance and occasional 'bony' pains felt during cold or rainy weather. From this point the disease usually pursues a benign course. Some patients with KS in the nodular form develop florid lesions usually on the foot. This lesion is a malignant tumor and if untreated, is fatal within 8-10 mo. In children less than 10 yr old KS is predominantly a disease of the lymph nodes. In young adults, 15-20 yr old, the gastrointestinal lesions are important and may be difficult to detect clinically. Three histologic subtypes of KS are recognized: mixed type, monomorphic (spindle cell) type, and anaplastic type. The first is most sensitive to chemotherapy while the latter two types are the more malignant forms. Bone erosion or destruction may occur. Lesions in the visceral organs usually remain silent. Few cases of KS have involved the brain. Two major categories of KS exist: indolent and aggressive varieties. (2 Refs)

11. KAPOSI'S SARCOMA IN HOMOSEXUAL MEN - A REPORT OF EIGHT CASES.

Hymes KB, Greene JB, Marcus A, William DC, Cheung T, Prose NS, Ballard H, Laubenstein LJ
(c/o Laubenstein), New York Univ. Medical Center, 530 First Ave., New York, NY, 10016
Lancet; 2(8247):598-600 1981

The clinical findings in eight young homosexual men in New York with Kaposi's sarcoma showed some unusual features. Unlike the form usually seen in North America and Europe, it affected younger men (4th decade rather than 7th decade); the skin lesions were generalized rather than being predominantly in the lower limbs, and the disease was more aggressive (survival of less than 20 mo rather than 8-12 yr). All eight had had a variety of sexually transmitted diseases. All those tested for cytomegalovirus antibodies and hepatitis B surface antigen or anti-hepatitis B antibody gave positive results. This unusual occurrence of Kaposi's sarcoma in a population much exposed to sexually transmissible diseases suggests that such exposure may play a role in its pathogenesis. (Author abstract) (12 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

12. TREATMENT OF DISSEMINATED MALIGNANT MELANOMA WITH HIGH-DOSE ORAL BCG.

Varella AD, Bandiera DC, De Amorim AR, Calvis LA, Santes IO, Escaleira N, Gentil F
Hospital A. C. Camargo Fundacao Antonio Prudente, Prudente, 211, 01509 Sao Paulo, SP, Brazil
Cancer; 48(6):1353-1362 1981

Thirty patients with unresectable disseminated melanoma (Stage IV) were treated with BCG (Moreau strain - Rio do Janeiro) by mouth, with weekly doses ranging between 200 mg and 28,000 mg. Five patients died in the first 2 mo of treatment. Of the remaining 25 patients, 2 (8%) showed complete regression, and 1 (4%) partial regression. Seven patients (28%) had stabilization of the disease for a 6-mo period, and 15 (60%) had progression of the disease. Complete and partial regressions were seen only in patients with extravisceral (sc) metastases, and were associated with a longer survival time. Regression of the sc metastatic nodules was always accompanied by the following local phenomena: increased temperature; local inflammation; softening, pain and pruritus at the nodule site; and a gradual decrease in size. At the site of the tumor mass, a hypochromic halo appeared. This halo remained permanently and was pathognomonic of the metastatic nodule rejection. When the halo was fully established, the inflammatory infiltrate was minimal and the malignant cells disappeared. If the area contained hairs, they underwent complete albinization. Serial biopsies of the nodules undergoing inflammatory changes and decreased consistency exhibited an intense cellular infiltration of lymphocytes, macrophages, and plasma cells around the malignant cells. This sometimes simulated lymphoid follicle formation involving the melanoma cells associated with necrosis in a centripetal way. Some patients with visceral metastases (particularly pulmonary) had an unexpectedly long survival, apparently associated with interruption of the growth rate of the masses. Eleven out of 20 deaths were due to cerebral metastases. When cerebral disease was diagnosed, BCG was discontinued and the administration of corticoids was usually associated with a disappearance of the inflammatory signs at the nodule sites, but with progression of the disease. Toxicity was minimal. (Author abstract) (37 Refs)

13. TRANSFER FACTOR IN THE TREATMENT OF HERPES SIMPLEX TYPES 1 AND 2.

Khan A, Hansen B, Hill NO, Loeb E, Pardue AS, Hill JM
Dept. Immunotherapy, Wadley Inst. Molecular Medicine, 9000 Harry Hines, Dallas, TX, 75235
Dermatologica; 163(2):177-185 1981

Transfer factor potentiates cellular immunity and induces interferon. It was because of these properties that transfer factor was tried in 17 patients with recurrent herpes simplex types 1 and 2. Transfer factor was administered in doses ranging from 5 to 10 U/m2 im. The interval between injections varied from 1 wk to 3 mo. Sixteen patients could be evaluated clinically in whom the recurrence rate decreased from 10.7 +-6.1 to 2.1 +-2.5 (mean SD). The reduction was statistically significant. Eight patients were completely free of disease while the other eight had a reduced number of episodes during the period of observation. Seven patients had abnormal T cell function as reflected by the low number of T cells or low lymphocyte transformation. Statistically significant improvement in the T cell function was observed. Delayed hypersensitivity skin test reactions also improved significantly. (Author abstract) (17 Refs)

CHEMOTHERAPY

14. PHASE II STUDY OF DIGLYCOALDEHYDE IN MALIGNANT MELANOMAS AND SOFT TISSUE SARCOMAS.

Vosika GJ, Briscoe K, Carey RW, O'Donnell JF, Perry MC, Budman D, Richards F, Coleman M
Dept. Medicine, Univ. North Dakota, c/o Veterans Admin. Hosp., Elm St N and 21st Ave., Fargo, ND, 58102
Cancer Treat Rep; 65(9):823-825 1981

A Phase II study of diglycoaldehyde was conducted in 42 patients with malignant melanoma and soft tissue sarcoma. All patients received diglycoaldehyde at a dose of 2 g/m2 iv over 6 hr daily for 3 days. This was repeated every 28 days. Major toxic effects included phlebitis and azotemia, requiring dialysis in one patient. Of the 42 patients, 38 were evaluable for response. One objective response occurred in a patient with malignant melanoma. Diglycoaldehyde at this dose and schedule appears to have no role in the management of malignant melanoma or soft tissue sarcoma. (Author abstract) (7 Refs)

15. EFFECT OF HIGH-DOSE THYMIDINE INFUSIONS IN PATIENTS WITH MYCOSIS FUNGOIDES.

Kufe DW, Wick MM, Moschella S, Major P
Div. Pharmacology and Medical Oncology, Sidney Farber Cancer Inst., 44 Binney St ., Boston, MA
Cancer; 48(7):1512-1516 1981

The antitumor effect of thymidine has been demonstrated in patients with leukemia and lymphoma. This report summarizes the treatment of three patients with mycosis fungoides, a chronic T-cell lymphoma. Four courses of thymidine (75 g/m2/day) were administered by continuous infusion for 4-7 days. Steady-state serum thymidine levels were in the range of 1-3 mM. Associated toxicities were minimal and consisted of mild headache and anorexia. Myelosuppression was manifested by transient declines in the peripheral WBC count. One patient had extensive clearing of diffuse erythematous plaques on the trunk and extremities that persisted for over 1 mo. A second patient had partial clearing of plaques that persisted for 2 wk following therapy and a third patient had a minimal response with 25% reduction in lymphadenopathy and noduloulcerative lesions. These responses indicate the effectiveness of thymidine as a single agent in the treatment of mycosis fungoides. (Author abstract) (17 Refs)

16. MANAGEMENT OF KAPOSI'S SARCOMA: CHEMOTHERAPY I.

Vogel CL
Div. Breast Cancer, Dept. Oncology, Univ. Miami Sch. Medicine, PO Box 016960, Miami, FL, 33101
Antibiot Chemother; 29:82-87 1981

A computerized search of the world literature for an association between Kaposi's sarcoma (KS) and chemotherapy revealed only 57 entries between 1970-1979. A unique variant of KS has been reported in association with immunosuppressive therapy used for other disease processes or to prevent graft rejection in renal heterotransplantation. Discontinuation of the immunosuppressive treatment may result in complete or significant regression of the KS. The most widely used chemotherapeutic agent for KS is vinblastine; vincristine is also widely used. Indolent nodular forms are probably responsive to vinblastine and possibly to chronic, low dose administration of alkylating agents or the nitrosoureas. Aggressive forms of KS (florid, infiltrative, or lymphadenopathic disease) probably require aggressive combination chemotherapy programs with the most effective combination being actinomycin D, vincristine and dacarbazine for actinomycin-resistant cases. A few cases have been treated with bleomycin, carmustine and ICRF-159 (razoxane). Adequately designed, controlled and randomized clinical trials should be conducted in centers with suitable expertise in African countries where the disease is endemic. (24 Refs)

17. MANAGEMENT OF KAPOSI'S SARCOMA: CHEMOTHERAPY II.

Olweny CL
Dept. Medicine, Makerere Univ. Medical Sch., Uganda Cancer Inst., Kampala, Uganda
Antibiot Chemother; 29:88-95 1981

Randomized clinical trials of patients with Kaposi's sarcoma (KS) treated with a three-drug combination (actinomycin D (ACT-D), vincristine (VCR), and imidazole carboxamide (DTIC)) were compared with those using a two-drug combination (ACT-D and VCR). Of the 40 patients treated with the two drugs, 22 (55%) achieved complete tumor regression (CR), 13 (32.5%) had partial response (PR), and 5 (12.5%) did not respond. Of the 32 receiving the three-drug combination, 30 (94%) achieved CR, 11 had PR and 1 had no response. The effectiveness of maintenance therapy in preventing or delaying disease relapse was investigated with further pulses of the three-drug combination every 3 mo up to 18 mo. or receive BCG immunotherapy by scarification. Another 1.5-2 yr will be required for completion. Of 27 male patients who received carmustine (BCNU), 9 had CR, 2 PR, and 16 no response. Of 47 patients (44 males, 3 females; aged 11-68 yr, av 42.1) treated with razoxane (ICRF 159), 10 achieved CR, 7 PR, 10 no response; 10 could not be evaluated. Other previous therapy had been received by 36/47. A protocol to maximize cell killing in KS involves VCR given to arrest dividing cells during mitosis; bleomycin to kill both dividing and nondividing cells; and ACT-D to inhibit recovery of G1 and S2 cells treated with the other two agents. Two patients with very aggressive, drug-resistant KS treated in this manner achieved CR; however, one experienced extensive exfoliative dermatitis. (10 Refs)

SURGERY

18. STAGING LAPAROTOMY IN CUTANEOUS T-CELL DISEASE.

Doyle JA, Winkelmann RK
Dept. Dermatology, Mayo Clinic and Mayo Foundation, Rochester, MN, 55905
Arch Dermatol; 117(9):543-546 1981

Staging laparotomy performed in 13 patients with various forms of cutaneous T-cell disease (mycosis fungoides, Sezary syndrome, cutaneous lymphoma, atrophic parapsoriasis, and alopecia mucinosa) showed evidence of visceral or lymph node involvement in three (23%) patients; in two of these patients, noninvasive investigations and staging procedures did not disclose any abnormalities. All three patients were alive after a mean follow-up period of 3 1/2 yr. In the 10 patients with normal findings at laparotomy, the presence of intra-abdominal lymphoma was suggested in six by noninvasive staging procedures (lymphangiogram, spleen or liver-spleen scan, and computerized tomographic scan of the abdomen). Five of these 10 patients died; 4 of the 5 patients died after relentless progression of the disease and visceral involvement. Staging laparotomy may have a role in the management of cutaneous T-cell disease because noninvasive investigations may be poor indicators of the presence or absence of intra-abdominal disease. The course of these patients, even those in whom laparotomies did not show any abnormalities, emphasizes the progressive potential of cutaneous T-cell disease. (Author abstract) (21 Refs)

OTHER THERAPEUTIC MODALITIES

19. CLINICAL EXPERIENCE WITH RADIOFREQUENCY HYPERTHERMIA.

Kim JH, Antich P, Ahmed S, Hahn EW
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Microwave Power; 16(2):193-197 1981

Clinical experience with radiofrequency (RF) hyperthermia in the treatment of various superficial malignancies is reported. For the RF techniques currently available, local hyperthermia can be achieved only for tumors that are superficial (depths of the order of 2 cm with typical applicators, up to 6 cm with cooling, multiple electrodes, movement of coils, etc). The presence of inhomogeneities must be considered in treatment planning. Thus, different anatomic locations require specialized applications. Temperature differentials between normal tissue and tumors are discussed. Preferential heating appears to be size dependent: smaller tumors are more difficult to heat. In a study involving 86 cancer patients (38 malignant melanoma, 15 mycosis fungoides, 6 lymphoma, 10 breast carcinoma, 3 chondrosarcoma, 14 other tumors), the overall complete tumor response rate following combination hyperthermia and radiation therapy (69/86, 80%) was superior to that obtained with radiotherapy alone (24/73, 33%). Important parameters for a successful control of the radioresistant tumors included a good thermal distribution within the tumor vol, a differential heating pattern between tumor and normal tissue, the radiation time dose fractionation schedules, and the sequence of combination therapy. Possibilities for future clinical studies are briefly discussed. (5 Refs)

MULTIMODAL THERAPY

20. THE RELATIVE EFFECTIVENESS OF RADIATION THERAPY, CORTICOSTEROIDS, AND SURGERY IN THE MANAGEMENT OF MELANOMA METASTATIC TO THE CNS SYSTEM.

Katz HR
Dept. Radiotherapy, American Oncologic Hosp., Central and Shelmire Streets, Philadelphia, PA, 19104
Int J Radiat Oncol Biol Phys; 7(7):897-906 1981

Various treatment modalities were studied retrospectively in patients with melanoma metastatic to the CNS. Among the 63 patients, 25 had multiple brain metastases (MBM) and 38 solitary brain metastases (SBM). The 41 males and 22 females ranged in age from 18-78 yr. Various antineoplastic agents were employed. Corticosteroids were given to 49 patients 2-7 days before radiation therapy (RT); 73% showed documented response to the agents, which was substantially higher than the 42% response rate to RT. RT led to response in 52% with

SBM and 30% with MBM. Large doses (500 rad or greater per fraction) produced significantly greater response than smaller doses, although fraction size had no effect on duration of response or survival. Surgical excision of SBM with RT had significantly longer av response (405 days vs 57 days) and survival (448 days vs 96 days) than did SBM who did not receive surgery. Second RT courses relieved recurrent neurological symptoms, but responses were short and without influence on survival. Four of seven patients with cord compression who underwent decompressive laminectomy showed neurological improvement; postoperative RT led to no further improvement. Two patients with cord compression who were paraplegic did not response to RT. Surgical excision with postoperative RT is recommended for management of SBM from melanoma. (34 Refs)

21. INTERSTITIAL HYPERTHERMIA AND INTERSTITIAL IRIDIUM 192 IMPLANTATION: A TECHNIQUE AND PRELIMINARY RESULTS.

Joseph CD, Astrahan M, Lipsett J, Archambeau J, Forell B, George FW
(c/o Lipsett) Div. Radiation Oncology, City of Hope Natl. Medical Center, 1500 East Duarte Road, Duarte, CA, 91010
Int J Radiat Oncol Biol Phys; 7(6):827-833 1981

The feasibility of combining interstitial hyperthermia (41-43 C, for 30-40 min) with interstitial Iridium 192 implantation (Ir-192, 2,000-3,000 rad) in the treatment of superficially accessible tumors has been tested on swine and confirmed in seven patients (3 with primary breast cancer, 1 with neck nodes from a tongue primary, and 3 with sc metastases from malignant melanoma or colon primaries). Therapy protocol consisted of external beam radiotherapy (3,000-4,000 rad in 3-4 wk), followed successively by 3 wk rest, the first hyperthermia session, Ir-192 implantation, and a second hyperthermia session. Techniques and instruments used for positioning the thermal probes and implants are described. (4 Refs)

CASE REPORTS

22. IGA NEPHRITIS ASSOCIATED WITH MYCOSIS FUNGOIDES. REPORT OF TWO CASES.

Ramirez G, Stinson JB, Zawada ET, Montamed F
Nephrology Section (111F), James A. Haley Veterans Admin. Hosp., 13000 N 30th St., Tampa, FL, 33612
Arch Intern Med; 141(10):1287-1291 1981

The association of mycosis fungoides and glomerulopathy previously has not been reported to our knowledge. Two patients with mycosis fungoides and recurrent microscopic hematuria underwent renal biopsy, which demonstrated a focal glomerulonephritis with preponderantly mesangial IgA deposition. The possible association between mycosis fungoides and IgA nephritis is reported. (Author abstract) (11 Refs)

23. FEBRILE NEUTROPHILIC DERMATOSIS ASSOCIATED WITH ACUTE LEUKEMIA.

Behm FG, Kay S, Aportela R
Medical Coll. Virginia, Box 597, Richmond, VA, 23298
Am J Clin Pathol; 76(3):344-347 1981

Febrile neutrophilic dermatosis (Sweet's Syndrome) is an uncommon syndrome characterized clinically by fever, neutrophilia, and erythematous, non-ulcerating papules or plaques on the face, neck, upper thorax, and extremities. A case associated with acute myelogenous leukemia is reported and nine other reported cases associated with acute non-lymphocytic leukemia are reviewed. The appearance and location of the lesions on the face, neck, upper trunk and extremities, a female predominance, an associated fever, marked dermal infiltrates of mature neutrophils, and rapid clearing of lesions with parenteral corticosteroids were manifestations similar to febrile neutrophilic dermatosis not associated with leukemia. Although the etiology of febrile neutrophilic dermatosis associated with acute leukemia is unknown, the resolution of lesions and symptoms with systemic corticosteroids and recurrence with relapse of leukemia suggests an immune process with the leukemic cell population serving as a possible antigenic source. (Author abstract) (17 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

24. INDUSTRIAL CARCINOGENESIS.

Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

The occurrence of carcinogens in the workplace, particularly as they relate to skin cancers, is reviewed. Such carcinogens include coal, tar, paraffin oil, lubricating oil, pitch, and creosote. Arsenic contamination in the air and water results from metallurgical processe. Arsenic also occurs in dyes, fruit-sprays, glass, and various other materials. X-rays, UV, and other electromagnetic radiation are carcinogenic. Single incidents of trauma can be accepted on a legal basis as carcinogenic, although they are more likely co-carcinogenic. Cutaneous carcinomas seem to require the interaction of a carcinogen and a co-carcinogen, such as UV or trauma, more than do organ-specific carcinomas. The applications of the British system of compensation in cases of exposure to carcinogens is discussed. (14 Refs)

25. MALIGNANT MELANOMA AMONG EMPLOYEES OF LAWRENCE LIVERMORE NATIONAL LABORATORY.

Austin DF, Synder MA, Reynolds PJ, Biggs MW, Stubbs HA
Resource for Cancer Epidemiology, State Dept. Health Services, 1450 Broadway, Oakland, CA, 94612
Lancet; 2(8249):712-716 1981

Nineteen cases of malignant melanoma (MM) were observed during 1972-77 among approx 5,100 employees of the Lawrence Livermore National Laboratory, where high energy physics research is conducted. This number was significantly higher (p less than 2 x 10(-6)) than that expected in a comparable age/race/sex/geographical segment of the population of the San Francisco Bay Area. That excess seemed to occur only among laboratory employees and not among the surrounding community, which suggests that an occupational factor is responsible. Preliminary case-comparison findings suggest that MM risk is not associated with length of employment at the laboratory nor with type of monitored radiation exposure. Although the data did not support an association between MM incidence and all scientific job classifications combined, an excess relative risk was observed among chemists. The reasons for the MM excess have not been identified. (Author abstract) (37 Refs)

SELECTED PRECLINICAL STUDIES

26. TILORONE-MEDIATED PROTECTION AGAINST MURINE B16 MELANOMA.

Turner EV, Wallace JH
(c/o Wallace) Dept. Microbiology and Immunology, Univ. Louisville Health Sciences Center, Louisville, KY, 40292
Proc Soc Exp Biol Med; 167(4):536-541 1981

The effects of tilorone hydrochloride (THC) on the growth of B16 murine melanoma was investigated. Mice were injected with 10(4) B16 cells and treated ip with 0.25 ml saline with or without 1 mg THC daily following tumor injection. Mice were observed for 90 days and tumor wt was obtained on day of death. THC-treated mice showed lower tumor incidence, increased survival time and lower av tumor wt than controls. All control groups had tumors and all died. During the period of observation, 40% of THC-treated mice did not develop tumors. In an in vitro study with B16 and C57Bl/6 fibroblasts, THC showed no selective toxicity for the B16 cells. Cell growth in these two cell types was not inhibited at THC concentrations from 0.5-0.05 ug/ml. A dose-response growth inhibition of THC-treated peritoneal exudate cells for B16 cells was observed. Adherent peritoneal exudate cells from THC-treated mice and products from such cells inhibited B16 growth in a dose-dependent manner. These results demonstrate that both cytotoxic effects and enhanced macrophage functions appear to have contributed to the reduced B16 melanoma growth observed in THC-treated animals. (26 Refs)

27. METASTATIC POTENTIAL CORRELATES WITH CELL-SURFACE PROTEIN ALTERATIONS IN B16 MELANOMA VARIANTS.

Rieber M, Rieber MS
Centre Microbiology and Cell Biology, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas 1010A, Venezuela
Nature; 293(5827):74-76 1981

Mice cell lines of differing metastatic potential in an in vivo assay (im injection into 9-12-wk-old C57BL mice of 2.5 x 10(4) cells from subconfluent cultures) were studied: B16-F10Lr cells (less than 5% pulmonary metastasis), B16-F10 cells (25-33% multiple lung metastases), and B16-BL6 (60-75% pulmonary metastasis); F10 cells were derived from F10Lr cells by successive in vivo/in vitro passaging, and BL6 cells were derived from F10 cells by selection for increased invasive capacity. Treatment with 1 M urea following enzymatic pre-iodination of cell-surface proteins and subsequent electrophoretic analysis showed low mol wt (approx 18,000 [18 K]) and high mol wt (approx 78 K) components from F10Lr cells, but only the high mol wt components from F10 cells. However, 8 M urea extracts of pre-iodinated F10Lr cells gave lower levels of the fast-migrating (18 K) protein, did not reveal the presence of several fast-migrating components, and showed the presence of slower-migrating components; this result may be due to the release or activation of a protease from the nonmetastatic cells by 1 M urea that may be inhibited by 8 M urea. Electrophoresis following the promotion of membrane vesiculation on surface proteins with p-formaldehyde and dithiothreitol revealed similar patterns in the two metastatic cell lines but a different pattern in the low-metastasis line; the latter showed an 18 K species, the absence of a 45 K species, and the presence of a significant species that migrated slightly faster than the 78 K species of the metastatic lines. Clones of the three cell lines at limiting dilutions revealed that the demonstrated differences were retained in the clones. Extraction of surface-iodinated cells with Triton-X followed by electrophoresis, revealed that the Triton-insoluble cell-surface components of the metastatic cell lines gave similar patterns with comparable amount of the 78 K species, the low-metastasis cell line had a greater level of radioactivity in the fast-migrating species. This is apparently the first report of cell-surface protein differences between cells of different metastatic potential. (16 Refs)

28. INHIBITION OF CLONOGENIC GROWTH OF MELANOMA CELLS BY COMBINATION OF MELANOCYTE STIMULATING HORMONE AND THEOPHYLLINE.

Wick MM
Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
J Invest Dermatol; 77(3):253-255 1981

The combination of MSH and theophylline is synergistic in inhibiting the growth as well as stimulating the differentiation of pigmented melanoma cells. In order to determine if a permanent alteration in the proliferative potential of these cells was achieved, we examined the effect of MSH and theophylline alone and in combination upon the plating efficiency and tumorigenicity of S-91 Cloudman melanoma cells. Following treatment with the combination of MSH and theophylline, the cells became deeply pigmented and had their colony forming ability reduced to 28% of control. Neither MSH or theophylline alone, although effective in reducing the growth rate of the cells, caused a significant reduction in clonogenic growth. When cells were pretreated with MSH and theophylline alone or in combination and reinjected into mice, the combination of MSH and theophylline caused a significant reduction in percentage of animals developing tumor (reduced to 14% of control). Cells treated with either MSH or theophylline alone were similar in their tumorigenic potential to control cells. These effects were selective since the nonmelanocytic control cells, mouse fibroblast L929 and Chinese hamster ovary when treated similarly did not exhibit any alteration in their clonogenic potential. The treatment of responsive cells with the combination of MSH and theophylline is capable of causing permanent decrease in the proliferative potential of murine melanoma cells and may have relevance to the treatment of this disease in man. (Author abstract) (12 Refs)

29. INHIBITION OF IN VITRO LYMPHOCYTE PROLIFERATION BY BRAIN GLYCOPROTEIN (NSA3) AND MESENCHYME-ASSOCIATED ANTIGEN (MAA).

Gilbert D, Delpech B, Chevrier A, Halavent C
U-78 INSERM, 543 chemin de la Breteque, F-76230 Bois-Guillaume, France
Cancer Immunol Immunother; 11(3):211-215 1981

Human peripheral blood lymphocytes were obtained from melanoma patients previously treated by BCG therapy and in remission. Cells were cultured in media containing various concentrations of phytohemagglutinin (PHA), Concanavalin A (ConA), pokeweed mitogen (PWM), or protein-purified derivative (PPD). Transformation of lymphocytes was studied in the presence and absence of brain glycoprotein (NSA3) or mesenchyme-associated antigen (MAA). Both NSA3 and MAA inhibited blastogenesis of lymphocytes in response to the mitogens PHA, ConA, and PWM, and to the antigen PPD. The optimum dose concentrations for NSA3 and MAA were 5 ug/ml/10(6) cells and 30 ug/ml/10(6) cells, respectively. Neither NSA3 nor MAA had any effect on control cultures not containing mitogens or antigens. No effect was noted on the mixed leukocyte response. The inhibitory effects of NSA3 and MAA thus were not due to cytotoxic effects. Extracts from liver and kidney tissue had no inhibitory effect. Evidently NSA3 and MAA have a suppressive action on a subpopulation of T lymphocytes. (25 Refs)

30. ANESTHETIC DRUGS ACCELERATE THE PROGRESSION OF POSTOPERATIVE METASTASES OF MOUSE TUMORS.

Shapiro J, Jersky J, Katzav S, Feldman M, Segal S
Dept. Surgery B, Shaare-Zedek Hosp., Jerusalem, Israel
J Clin Invest; 68(3):678-685 1981

Experiments were made to investigate the effect of four anesthetic drugs that are commonly used in surgical practice on the postoperative growth of mouse tumors in syngeneic recipients. These experiments revealed that some of the anesthetics when applied for surgical excision of the local tumor, strongly accelerated postoperative progression of spontaneous lung metastases produced by the 3LL Lewis lung carcinoma and by the B16 melanoma. Some of the drugs caused the appearance of metastases in organs, such as the liver, in which spontaneous metastases are not usually produced by these tumors. A T10 sarcoma clone that does not produce detectable metastases in immune intact mice even following iv injection, did produce metastases when injected into animals treated with pentothal sodium. (Author abstract) (27 Refs)

31. ISOLATION AND PARTIAL CHARACTERIZATION OF A MUCIN-TYPE GLYCOPROTEIN FROM PLASMA MEMBRANES OF HUMAN MELANOMA CELLS.

Umemoto J, Bhavanandan VP, Davidson EA
(c/o Bhavanandan) Dept. Biological Chemistry, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Biochim Biophys Acta; 646(3):402-410 1981

Plasma membranes were isolated from HM7 melanoma cells grown in the presence of [3H]glucosamine and Na35/2SO4 or [3H]mannose and [14C]glucosamine. The labeled glycoconjugates were solubilized with 0.6 M lithium diiodosalicylate/ 0.5% Triton X-100. Fractionation of glycoconjugates by repeated chromatography on columns of Sepharose CL-6B and DEAE-Sepharose and by affinity chromatography on WGA-Sepharose yielded three radiochemically homogenous glycoproteins. One of these having an apparent mol wt of 100,000 was found to contain clusters of (AcNeu)1 or 2--[Gal--GalNAc] linked O-glycosidically to the protein. One other glycoprotein contained both O-glycosidically and N-glycosidically-linked oligosaccharides, and the third contained only N-glycosidically-linked carbohydrates. Preliminary results indicate that the 100,000 mol wt mucin-type glycoprotein is present in significantly reduced quantities in cultured human fetal uveal melanocytes. Further, the bulk of the glycoproteins from the melanocytes were of lower molecular size compared to those from the melanoma cells. (Author abstract) (33 Refs)

32. ESTABLISHMENT OF PIGMENTED MELANOCYTE CULTURE STRAIN FROM HARDING-PASSEY MELANOMA.

Takematsu H, Maruyama T, Kataoka S, Seiji M
Dept. Dermatology, Tohoku Univ. Sch. Medicine, Sendai 980, Japan
Tohoku J Exp Med; 134(3):339-340 1981

The procedure for establishing a pigmented cell strain from melanotic Harding-Passey melanoma is described and the morphological characteristics of the established strain are reported. The strain retained melanin-forming ability after long cultivation in the system. This cell strain should be useful for studies on melanogenesis and pigment degradation and the comparison with other melanoma cells in vitro may allow for analysis of melanosome formation. (4 Refs)

33. INCREASED PHOSPHOTYROSINE CONTENT AND INHIBITION OF PROLIFERATION IN EGF-TREATED A431 CELLS.

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Dept. Medicine, Div. Endocrinology, Univ. California San Diego, Sch. Medicine, La Jolla, CA, 92093

Nature; 293(5830):305-307 1981

The effect of epidermal growth factor (EGF) on phosphotyrosine content of exponentially growing A431 human epidermoid carcinoma cells was determined by labelling cells to equilibrium with 32P-orthophosphate, treating replicate plates 3 hr with EGF, and measuring phosphotyrosine. EGF increased phosphotyrosine content 7x from 0.02 to 0.14% of cellular phosphoamino acids, indicating that EGF activates tyrosine-specific protein kinase activity in vivo as it does in vitro and the kinase activity is an important component of the mechanism of EGF action. In contrast to Rous sarcoma virus (RSV) transformation, EGF inhibits replication of A431 cells. No growth was apparent when A431 cells were maintained with saturating concentrations of EGF over a 14-day period. Affinity of EGF receptors for EGF was inversely related to cell density. The measured equilibrium dissociation constant, Kd, for EGF binding at low and high cell densities was higher than the half-maximally effective concentration, EC50, of EGF required to inhibit cell proliferation at that cell density (7x at 500 cells/square cm and 4x at 15,000 cells/square cm). Occupancy of only a fraction of EGF receptors seems to be required for growth inhibition. Dose-response of growth inhibition was strongly affected by tissue culture substratum. (36 Refs)

34. GLUCOCORTICOIDS AND BENZO(A)PYRENE HAVE OPPOSING EFFECTS ON EGF RECEPTOR BINDING.

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Nature; 293(5831):404-406 1981

Epidermal growth factor (EGF)-receptor binding was used as a marker for membrane effects in C3H10T1/2 mouse embryo fibroblasts exposed to the potent glucocorticoid fluocinolone acetonide (FA), and to the carcinogens benzo(a)pyrene (BP), and 12-O-tetradecanoyl-phorbol-13-acetate (TPA). FA alone produced a 1.9x stimulation of EGF-receptor binding over that observed in control cultures. The stimulation was apparent within 1 hr and reached a max by 24 hr. FA pretreatment (2 x 10(-7) M) protected the cells from the approx 50% inhibition of EGF-binding induced by BP (2 x 10(-6) M) or TPA (10(-9) M). Results suggested that glucocorticoids inhibit carcinogenesis by inducing cell membrane changes that are reciprocal to those induced by carcinogens and tumor promotors. (22 Refs)

35. SIMILARITIES BETWEEN FIBROBLAST-DERIVED GROWTH FACTOR AND PLATELET-DERIVED GROWTH FACTOR.

Dicker P, Pohjanpelto P, Pettican P, Rozengurt F
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Exp Cell Res; 135(1):221-227 1981

Platelet-derived growth factor (PDGF), one of the most potent mitogens in serum for non-transformed cells, shares many biological and physical properties with fibroblast-derived growth factor (FDGF), a polypeptide produced by BHK cells transformed by SV40. Thus FDGF and PDGF have biological activity which is recoverable from sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, at positions indicating similar mol wt. Further, the biological activity of both factors is heat-stable but sensitive to mercaptoethanol. FDGF and PDGF have similar abilities to induce DNA synthesis synergistically in the presence of either insulin, epidermal growth factor (EGF), vasopressin or colchicine. In contrast to other growth factors, (i) either FDGF or PDGF can induce DNA synthesis in the absence of other mitogens in 3T3 cells maintained in serum-free medium and (ii) a transient exposure of cultures to FDGF or PDGF causes a persistent stimulation of DNA synthesis. Either FDGF or PDGF enhances colony formation of non-transformed cells cultured in suspension in the presence of EGHF and serum. FDGF is not PDGF adsorbed by SV40-BHK cells from serum, since SV40-BHK cells plated and grown in the absence of serum still produce FDGF. In view of the similarities between PDGF and FDGF, we suggest that they may belong to the same family of growth factors. (Author abstract) (20 Refs)

36. LIGHT-INDUCED CHROMATID DAMAGE IN HUMAN SKIN FIBROBLASTS IN CULTURE IN RELATION TO THEIR NEOPLASTIC POTENTIAL.

Parshad R, Gantt R, Sanford KK, Jones GM, Camalier RF
Dept. Pathology, Coll. Medicine, Howard Univ., Washington, DC, 20059
Int J Cancer; 28(3):335-340 1981

Skin fibroblasts from ataxia telangiectasia and xeroderma pigmentosum (XP) donors and from the XP sib (possible heterozygote), all genetically predisposed to a high risk of cancer, show an increased susceptibility to light-induced chromatid breaks after culture in vitro. Light-induced chromatid breaks were shown previously to result from generation of hydrogen peroxide (H2O2) during light exposure. The level of susceptibility attained is significantly higher than that observed in 13 lines of fibroblasts from normal skin of donors ranging in age from 3 days to 92 yr or from fetal skin tested at various population doubling levels. Two lines of normal skin fibroblasts transformed by chemical carcinogens to neoplastic cells also show a significant increase in susceptibility as compared with their untransformed controls. These data indicate for human cells, as reported earlier for mouse cells, an association between enhanced susceptibility to light-induced chromatid damage and neoplastic potential; this association is further supported by the high susceptibility of cells derived from a human adenocarcinoma. Two observations are consistent with the concept that the increased susceptibility does not result from greater initial damage to the DNA of the neoplastic cells. First, activities of the ubiquitous H2O2 scavenging enzyme, glutathione peroxidase, are similar in the paired normal and neoplastic cell populations. Second, cells of the paired lines are equally sensitive to DNA breakage by exogenous H2O2. The enhanced susceptibility associated with neoplastic potential may result from an impaired capacity to repair DNA rather than a greater initial sensitivity of the neoplastic cells to the damaging agent. (Author abstract) (35 Refs)

37. ENHANCED REACTIVATION OF ULTRAVIOLET-DAMAGED HERPES VIRUS IN ULTRAVIOLET PRETREATED SKIN FIBROBLASTS OF CANCER PRONE DONORS.

Coppey J, Menezes S
Institut Curie, Section de Biologie, 26 rue d'Ulm, 75231 Paris Cedex 05, France
Carcinogenesis; 2(8):787-793 1981

The enhanced reactivation (ER) of UV-damaged nuclear replicating DNA viruses was studied in host cells treated with UV prior to infection. Host cells were from normal (N), xeroderma pigmentosum (XP), excision proficient XP (XP variant), xerodermoid (XD), XP heterozygote (XH), epidermodysp lasia verruciformis (EV), and miscellaneous donors. Cells received 260 nanom UV radiation (0.1-25 Joules/square meter [m2]) 0-60 hr before infection with intact (HSV) or UV-irradiated herpes simplex virus (UV-HSV). ER was max for all cell lines when the interval between irradiation of the host cells and infection with virus was 36 hr. In N, XH, XD, XP variant, EV Mibelli's porokeratosis, diffused nevomatosis, and Down's syndrome cell lines, ER was max at a UV dose of 15 Joules/m2. In XD, EV, and XP variant cells the ER was increased 10-fold over the ER in N cells. Max ER was obtained in three groups of XP cells with UV doses of 0.1, 0.3, and 2 Joules/m2. The results demonstrate that UV-HSV undergo ER when host cells are exposed to UV prior to infection. The ER is apparently brought about by an as yet undescribed transitory DNA repair mechanism in the host cells. (54 Refs)

38. INCREASED LEVELS OF NEURON-SPECIFIC ENOLASE IN PC12 PHEOCHROMOCYTOMA CELLS AS A RESULT OF NERVE GROWTH FACTOR TREATMENT.

Vinores SA, Marangos PJ, Parma AM, Guroff G
Section on Intermediary Metabolism, Lab. Developmental Neurobiology, Natl. Inst. Child Health and Human Development, Bethesda, MD, 20205
J Neurochem; 37(3):597-600 1981

Treatment of PC12 pheochromocytoma cells with nerve growth factor (NGF) resulted in increased levels of neuron-specific enolase (NSE). Neither insulin, growth hormone, cytochrome c, nor sodium butyrate increased NSE levels. *Epidermal growth factor* (EGF) did increase NSE levels, although not to the same extent as NGF. As little as 1 ng/ml NGF induced the max increase in NSE. As PC12 cells increased in density, the NSE levels increased even in untreated cells. (Author abstract) (24 Refs)

39. EFFECTS OF 12-O-TETRADECANOYL PHORBOL-13-ACETATE AND EPIDERMAL GROWTH FACTOR ON THE PROLIFERATION OF HUMAN MUTANT FIBROBLASTS IN VITRO.

Gansler T, Kopelovich L
(c/o Kopelovich), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Lett; 13(4):315-323 1981

The role of cell density in the response of cultured skin fibroblasts (SF) from individuals with hereditary adenomatosis of the colon and rectum (ACR) and from normal individuals to 12-O-tetradecanoyl phorbol-13-acetate (TPA) and to epidermal growth factor (EGF) was examined. The effect of TPA and

EGF on the morphology of cell clones was also studied. Treatment of high density (6 x 10(4) cells/square cm) ACR-SF cultures with TPA produced dose-dependent stimulation of cell proliferation over the entire (0.5-100 nanog/ml) range tested. Addition of TPA to sparse (4.75 x 10(3) cells/square cm) cultures resulted in biphasic dose-response, with max inhibition at 2.0-10 nanog/ml. Similar results were found with normal human SF, primarily in sparse cultures, but these cells were more sensitive than ACR-S F. Normal SF in dense culture were not responsive to TPA stimulation. EGF (0.01-10 nanog/ml) was mitogenic in both sparse and confluent ACR-SF cultures in a dose-dependent manner. At EGF levels above 50 nanog/ml, however, inhibition of cell proliferation became apparent. Normal SF responded similarly. TPA exposure induced formation of dendritic-like cells with irregular thin cytoplasmic processes in both cell types. ACR-SF exposed to EGF were more densely packed and spindle-shaped, with more parallel orientation in the periphery. The results suggested that EGF and TPA share one of two existing TPA receptors; the higher affinity (unshared) receptor becomes saturated at ligand concentrations below 10 nanog/ml. TPA inhibition in sparse culture reflects the extent of neoplastic transformation; the less sensitive tumor cells apparently lack the higher affinity receptors. (26 Refs)

40. ESTABLISHMENT OF A CELL LINE OF HUMAN SKIN SQUAMOUS CELL CARCINOMA IN VITRO.

Kondo S, Aso K
Dept. Dermatology, Yamagata Univ. Sch. Medicine, Yamagata-city, Yamagata, 990-23, Japan
Br J Dermatol; 105(2):125-132 1981

A cell line of a squamous cell carcinoma of human skin (HSC-I) has been established in vitro, and successfully maintained proliferative in continuous tissue culture for about 2 1/2 yr since March 1978. Another cell line (HSC-Ib) has been established in vitro from the recurrence of the same cancer. It has been maintained for about 8 mo since December, 1979. 3T3 feeders were used in the initial cultures in both cases. The cells grow in a monolayer in vitro and are epithelioid with anaplastic features. Chromosome analysis of HSC-I, frozen and thawed HSC-I, the transplanted tumor in a nude mouse and HSC-Ib all showed hypotetraploidy with the modal number 80, which reconfirms that HSC-I derives from the original skin tumor. The cell line is available to other investigators. (Author abstract) (14 Refs)

41. A NEW SMALL (40 KD) KERATIN FILAMENT PROTEIN MADE BY SOME CULTURED HUMAN SQUAMOUS CELL CARCINOMAS.

Wu YJ, Rheinwald JG
Div. Cell Growth and Regulation, Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Cell; 25(3):627-635 1981

We examined the keratin proteins of nine cell lines cultured from human squamous cell carcinomas (SCCs) of the epidermis and oral epithelium. All of these lines contained the four major keratins (46 kd, 50 kd, 56 kd, and 58 kd) found in normal keratinocytes cultured from these epithelia. A 40 kd protein was also present in the Triton-insoluble cytoskeletal fraction of three of the lines. The 40 kd protein had an isoelectric point of 5.3, near that of the 46 kd and 50 kd keratins. It was precipitated by an antiserum against total s corneum keratins, and also by an antiserum against purified 46 kd keratin. An antiserum raised against the purified 40 kd protein had a higher titer against the 40 kd protein, detected by immunoprecipitation, and did not crossreact with the 46-58 kd keratins. The anti-40 kd serum stained, by indirect immunofluorescence, a cytoplasmic filament network in cells of the SCC lines that synthesize the 40 kd protein. These filaments were of a pattern indistinguishable from that stained by antiserum against total s corneum keratins, and the pattern was not altered by pretreatment of the cells with colcemid. The anti-40 kd serum did not stain the SCC lines that do not synthesize the 40 kd protein; normal human newborn foreskin keratinocytes or fibroblasts; or 3T3, HeLa or XB cells. Keratinocytes cultured from uninvolved epidermal or oral tissue of patients whose tumors had given rise to SCC lines that synthesize the 40 kd protein were also not stained by the anti-40 kd serum. Synthesis of the 40 kd protein was greatly reduced in tumors formed by the SCC lines that make this protein in culture. Partial proteolytic digestion maps of the 40 kd protein were unique, but very similar to those of the 46-58 kd keratins. These results constitute strong evidence that the 40 kd protein is a keratin, and is neither a breakdown product nor an incomplete translation product of a gene for one of the larger keratins. It is the smallest epidermal keratin yet to be described. The 40 kd keratin may be the product of a normally unexpressed gene or transcript that often becomes activated during the course of keratinocyte transformation. Like the larger keratins, the level of its expression is regulated and is different in cells growing in vivo and in culture. (Author abstract) (37 Refs)

REVIEWS

42. PAPILLOMAVIRUS AND CUTANEOUS MALIGNANCY.

Bender ME, Pass F
Dept. Dermatology, University Hospitals, Box 98, 420 Delaware St. S.E., Minneapolis, MN, 55455
Int J Dermatol; 20(7):468-474 1981

The relationship between papillomaviruses and malignancy in both the human and animal systems is reviewed. The structure, classification, and host-specificity of human papillomavirus (HPV) and the development and transmission of HPV-related warts are reviewed. The oncogenic conversion of papillomavirus-induced animal tumors, as studied in the rabbit and bovine systems, is reviewed. The Shope papilloma, a virus-induced epidermal neoplasm which is indigenous to western cottontail rabbits in the Mississippi River Valley, is discussed. The incidence of malignant degeneration of Shope papillomas is considered. In addition to the oncogenic potential of the virus alone, other factors including host genetic composition and extrinsic chemicals seem to be a factor in malignant conversion. The relationship between HPV and epidermoid carcinoma is discussed. Abnormalities, including epidermodysplasia verruciformis, laryngeal carcinoma developing from multifocal juvenile laryngeal papillomas, bowenoid papulosis, genital carcinoma in situ, and verrucous carcinomas, are discussed in relation to HPV. (88 Refs)

43. THE DIAGNOSIS AND TREATMENT OF MYCOSIS FUNGOIDES (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
The Diagnosis and Treatment of Mycosis Fungoides (Oncology Overview) Wolf, J E, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922805:; OT-81/05:44pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. This Overview covers all clinical and preclinical aspects of mycosis fungoides. It includes clinical sections on the classification, diagnosis, and management of this disorder as well as etiology and epidemiology, preclinical research, and reviews of the literature.

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MELANOMA AND OTHER SKIN CANCER

Diagnosis, Treatment

SERIES CT22 No. 82/03

MARCH, 1982

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DIAGNOSIS

1. PROGNOSTIC HISTOPATHOLOGICAL FEATURES OF MALIGNANT MELANOMA. NEW STATISTICAL APPROACHES.

Le Doussal V, Brunet M, Guerin P, Hacene K, Lasry S, Marcotorchino F, Michaud P, Hebert H, Gest J

Centre Rene-Huguenin, 5, rue Gaston-Latouche, F 92211 Saint-Cloud, France

Nouv Presse Med; 10(31):2561-2563 1981

In a study of 155 cases of malignant melanoma, the most significant prognostic variables were determined. Men were 3x more likely to die from the disease than women. The probability of metastases and death was 3x greater for nodular melano-

HE 20. 3173/2:

mas. The extent of invasiveness, cellular type, and the degree of mitotic activity were determined significant. Tumor thickness was the most important prognostic factor because it correlated with the incidence of recurrence, metastases, and death. Of 25 patients with lesions less than or equal to 0.75 mm, 21/25 were alive without recurrence or metastases. Of 29 patients with lesions greater than 3 mm, 18 had died and 3 were alive with recurrent lesions. The Breslow classification of tumor thickness (4 classes) were used in the study. It is suggested that such a classification be used to determine therapeutic approaches and prognoses in cases of malignant melanoma. (8 Refs) (In FRE)

2. RELIABILITY OF ULTRASONIC DIFFERENTIATION OF CHOROIDAL MELANOMAS FROM HEMANGIOMAS (MEETING ABSTRACT).

Poujol J, Le Roy M, Toufic N
No affiliation given
Excerpta Med Int Congr Ser; 547:136 1981

The aim of this study was to evaluate the reliability of the differential diagnosis between choroidal melanomas and angiomas using echography. It includes verified choroidal melanomas and hemangiomas examined in A-mode and contact B-mode over the past 6 yr. The tumors examined in A-mode only over the past 17 yr were not included. The various differential criteria are described and their diagnostic worth evaluated. The conclusion reached is that echography is an extremely valid method for differentiating between a malignant tumor such as a choroidal melanoma and a benign tumor such as an hemangioma, as long as the swelling is 2.5 mm or more. The prognosis and treatment depend on this diagnosis. (no Refs)

3. CAVERNOUS HEMANGIOMAS OF THE CHOROID (CLINICAL REVIEW OF 10 CASES).

Bonnet M, Francoz-Taillanter N
No affiliation given
Bull Soc Ophtalmol Fr; 81(4/5):455-458 1981

The diagnosis of choroidal cavernous hemangiomas (CCH) in 10 patients (7 males, 3 females; 11-60 yr old) is reviewed. All ten patients presented with a macular syndrome. Of the 10 patients, 6 were initially diagnosed as having ***malignant melanomas.*** The site, shape, and dimensions of the tumors are described. Fluorescent angiography showed the characteristic signs of a CCH for all patients: a grossly visible vascular network in the choroid and retina, diffusion in the area of the tumor at the arterial and venous level of the retina, and a delayed intraretinal accumulation of coloration with a microcystic appearance in relation to the hemangiomas. Before the injection of dye, the hemangiomas were recognizable by their yellow-orange coloration. In infrared absorption angiography, after the injection of indocyanine green, the tumor showed progressive and uniform green coloration. The coloration was max in the retinal veins. The coloration persisted after the disappearance of color from normal retina and choroid vessels. Two patients were treated by enucleation before the diagnosis of malignant melanoma was ruled out. Two patients refused treatment. Of the six patients treated with argon laser photocoagulation two required cryotherapy. After treatment, vision was improved in 4/6 patients and unchanged in 2/6, while chromatic vision and the visual field were improved in 5/6. Serous retinal detachment and macular edema resolved after treatment in 4/6 patients. (4 Refs) (In FRE)

4. PLASMA LIPID-BOUND SIALIC ACID AND CARCINOEMBRYONIC ANTIGEN IN CANCER PATIENTS.

Dnistrian AM, Schwartz MK
Dept. Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Clin Chem; 27(10):1737-1739 1981

We evaluated lipid-bound sialic acid as a 'marker' in cancer patients and assessed the individual and combined value of lipid-bound sialic acid and carcinoembryonic antigen determinations in these patients. Plasma was sampled from 62 normal subjects and 125 cancer patients. Lipid-bound sialic acid was determined by the resorcinol method after total lipid extraction and isolation of the sialolipid fraction from plasma. Neither marker was increased in many breast cancer patients. Carcinoembryonic antigen was increased more commonly and to a greater degree in colon cancer patients and seems to be the preferred marker. Both markers were increased in lung cancer patients and their combined evaluation improved the rate of detection. Lipid-bound sialic acid was increased in more patients with leukemias, lymphomas, Hodgkin's disease, and ***melanomas,*** suggesting that it may be a useful biochemical marker in these types of cancer. (Author abstract) (8 Refs)

5. CYCLIC NUCLEOTIDE PHOSPHODIESTERASES IN NORMAL AND MALIGNANT HUMAN TISSUES.

Stefanovich V, Ambrus JL, Ambrus CM, Karakousis C, Takita H
(c/o J. L. Ambrus), Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(4):243-250 1981

Biopsy samples were obtained from tumor tissue and surrounding normal tissue from the same organs of the same patients in 25 patients. Adequate studies could be performed on all parameters in 18 tissue pairs: 12 malignant ***melanomas,*** 4 sarcomas, and 2 others. Significantly higher levels of cAMP low affinity phosphodiesterases were found in the tumors as compared to the controls. Similar differences were seen in the high affinity cAMP phosphodiesterases, but these were of borderline significance. High affinity cGMP phosphodiesterase levels did not differ significantly between normal and neoplastic tissue samples. Low affinity cGMP phosphodiesterases were not detectable in either tissues. These studies together with earlier experimental findings suggest possible auxiliary therapeutic trials with phosphodiesterase inhibitors. (Author abstract) (36 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

6. PROSTAGLANDIN MODULATION OF ADCC IN HUMAN MALIGNANT MELANOMA (MEETING ABSTRACT).

Murray JL
Oklahoma Medical Research Foundation, Oklahoma City, OK
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The effect of prostaglandin E2 (PGE2) inhibitors, indomethacin (I) and anti-PGE2 antibody (PGE2-Ab), on monocyte (M) as well as lymphocyte (L) antibody dependent cytotoxicity (ADCC) was studied in 16 malignant melanoma patients (MM) and 12 controls (C). Patients were receiving adjuvant immunotherapy with sq Corynebacterium parvum. M and L were separated by adherence techniques into M enriched and L enriched fractions and incubated in triplicate for 4 hr with 51Cr labeled anti-D coated O positive human (H)RBC at various effector to target (E:T) ratios. C parvum significantly increased M-ADCC in patients compared to control M-ADCC at E:T of 1:2. L-ADCC was not affected. The addition of I to the assay significantly increased individual M-ADCC in 7 MM, but not in 9 C. A similar trend was seen with PGE2-Ab. L-ADCC was not affected by I in MM or C even at E:T of 5:1. M-ADCC in 5 C was also not affected at this ratio implying that M preactivation rather than E:T ratio is the important factor. Similar increases were seen if M were first preincubated with PGE2-Ab for 30 min, washed, and incubated with HRBC (3 pts). The increase seen was linear over the 4 hr time course. These data suggest: (1) PGE2 acts as a feedback mechanism to limit activated M-ADCC, (2) PGE2 is produced by adherent cells, (3) inhibition follows an early triggering event and does not require the continuous presence of inhibitor, (4) the kinetics of ADCC are not changed. (no Refs)

7. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY FOR CULTURED AUTOLOGOUS MELANOMA CELLS.

Livingston PO, Michitsch R, Shiku H, Pinsky CM, Oettgen HF
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cell Immunol; 64(1):131-143 1981

Sera from 33 patients with malignant melanoma were tested for antibody-dependent cell-mediated cytotoxicity (ADCC) against cultured autologous melanoma cells prelabeled with [3H]proline in a 36-hr assay. Effector cells (autologous or from normal donors) were obtained by Ficoll-Hypaque separation of peripheral blood. Assay sensitivity (but not specificity) was affected by the effector cells used, the optimal source of effector cells varying between different autologous serum-target cell combinations. The activity of autologous effector cells appeared to correlate inversely with the extent of disease. Sera from 18 patients gave positive direct tests. In seven cases reactivity was strong enough to permit analysis of specificity with absorption tests. Serum from one patient recognized a melanoma antigen restricted to autologous melanoma cells and three other melanoma cell lines, and not present on other melanoma cel l lines or autologous tissues, nonmelanoma tumor cells, or xenogeneic cells. Sera from five patients detected a diverse group of widely distributed antigens, all related to fetal calf serum (FCS). Serum from the seventh patient reacted with a widely distributed antigen not related to FCS. (Author abstract) (21 Refs)

8. DIFFERENTIAL EFFECTS OF INDOMETHACIN AND PGE2 ON THE DEPRESSED MITOGEN RESPONSES OF CANCER PATIENTS (MEETING ABSTRACT).

Tilden AB, Dougherty PA, Balch CM
University of Alabama in Birmingham, Birmingham, AL
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The influence of prostaglandin E2 (PGE2)-producing suppressor cells on depressed mitogen responses were studied in 78 patients with head and neck (H and N) cancer and with melanoma. Indomethacin (at 1ug/ml) significantly enhanced the blastogenic responses to phytohemagglutinin and Concanavalin A by peripheral blood mononuclear cells (PBMC) from both H and N patients and melanoma patients compared to 73 controls. However, the restorative effect of indomethacin did not correlate directly with PGE2-production. After a 48 hr culture, PBMC from 10 H and N cancer patients produced excessive amounts of PGE2 compared to 36 normal individuals, while PGE2 production by PBMC from 12 melanoma patients was similar to the normal controls. Furthermore, lymphocyte sensitivity to PGE2 for melanoma patients was essentially the same as normal controls since exogenous doses of PGE2 suppressed the mitogen responses to the same degree. Since indomethacin has multiple effects on cellular metabolism, a structurally unrelated inhibitor of PGE2 synthesis (RO-205720, LaRoche) was also tested. This drug (at 20ug/ml) enhanced the blastogenic responses of H and N cancer patients, but had little or no effect on the mitogen responses of melanoma patients. Indomethacin thus acts as an immunomodulator in both H and N cancer and melanoma patients. In the H and N cancer patients indomethacin blocks excessive PGE2 production. In contrast, the indomethacin enhancement of mitogen responses in melanoma patients is unrelated to PGE2-mediated suppression. (no Refs)

9. CLINICAL EXPERIENCE WITH AUTOBIOTHERAPY OF MALIGNANT TUMOR DISEASE: A PRELIMINARY REPORT.

Ngu VA, Titanji VP, Muna D, Nyoth J, Lekeuagni C
Cancer Res. Lab., Univ. Centre Health Sciences, Univ. Yaounde, Yaounde, Cameroun, Africa
J Natl Med Assoc; 73(10):927-937 1981

The peripheral WBC of 27 malignant tumor patients were activated separately by incubation in a serum-free medium containing the respective tumor cells or material. The effect of the injection of the activated WBC or their products, termed tumor WBC cultures (TLC), was studied in five patients with Kaposi sarcoma, five with carcinoma of the breast, four with carcinoma of the cervix, three with soft tissue sarcoma, two with carcinoma of the maxillary antrum, and a miscellaneous group of six patients. In 52% of cases, there was significant tumor regression. Tumor regression was most marked in patients with ***Kaposi sarcoma,*** carcinoma of the cervix, pharynx, and pancreas, one patient with a slow growing fibrosarcoma, one patient with a metastatic breast carcinoma, and also in one patient with myelogenous leukemia. However, not all the types of tumor studied responded satisfactorily to autobiotherapy. The reasons for the differences in response to autobiotherapy remain to be determined. Even so, the positive results obtained indicate that autobiotherapy is worthy of further research as an alternative in controlling malignant tumor disease. (12 Refs)

CHEMOTHERAPY

10. HIGH-DOSE MELPHALAN IN ADVANCED MALIGNANT MELANOMA (MEETING ABSTRACT).

Rustin GJ, Cornbleet MA, Hedley DW, McElwain TJ
Department of Medicine, The Royal Marsden Hospital and Institute of Cancer Research, Downs Road, Sutton, Surrey, England
Br J Cancer; 43(5):719 1981

Twenty-seven patients with symptomatic or life-threatening metastases from malignant melanoma were treated with high-dose melphalan (greater than 140 mg/m(2)) and autologous marrow rescue. Fourteen of these patients also received cyclophosphamide (500 mg) iv 7 days before the melphalan. These maneuvres reduced the gut and marrow toxicity of the melphalan, so that doses up to 260 mg/m2 could be tolerated. Objective tumor regression was obtained in 20/27 (74%) of the patients with 12/27 (44%) showing a decrease in the product of 2 diameters of all measurable lesions of greater than 50% of whom 2/27 (7%) entered complete remission. This compares with a regression rate of only 9% when conventional doses of melphalan are used. Overall there was no survival benefit for those whose tumors regressed compared to those with no response. However, life-table analysis showed that median survival for the 9 patients who received greater than 200 mg/m2 of melphalan having previously been primed was 11 mo from treatment and 14 mo from dissemination, compared with 3 and 8 mo respectively for those who received less than 200mg/m2 of melphalan. (1 Ref)

11. TREATMENT OF MALIGNANT MELANOMA BY INTRAVASCULAR 4-HYDROXYANISOLE.

Morgan BD, O'Neill T, Dewey DL, Galpine AR, Riley PA
Univ. Coll. Hosp., Gower St., London WCI, England
Clin Oncol; 7(3):227-234 1981

Regression of localized malignant melanomas treated by ia infusion of 4-hydroxyanisole (4-OHA) is reported. No generalized toxic effects of 4-OHA were observed. Iv administration of the drug was not therapeutically effective. (Author abstract) (13 Refs)

SURGERY

12. REGIONAL LYMPH NODE MANAGEMENT AND OUTCOME IN 100 PATIENTS WITH HEAD AND NECK MELANOMA.

Olson RM, Woods JE, Soule EH
(c/o Woods) Section Publications, Mayo Clinic, Rochester, MN, 55905
Am J Surg; 142(4):470-473 1981

One hundred patients with invasive melanoma of the head and neck were treated by one surgeon from 1970 to 1978. Lymph node dissections were performed in 77 patients for palpable adenopathy, local recurrence, or tumor thickness greater than 0.75 mm when measured by micrometry. No patient whose lesion was less than 1.0 mm thick had a local recurrence or died as a result of melanoma. Patients who underwent elective lymph node dissection with findings of up to two positive nodes had a 53 to 56% 5 yr survival rate, while those with three or more nodes had a poor prognosis (15% 5 yr survival rate). The patterns of recurrence showed that relapse after nodal dissection usually presented with systemic metastases. The data support a therapeutic scheme based on 2 to 5 cm wide excision alone for lesions less than 0.75 mm in thickness and elective nodal dissection for specific indications. (Author abstract) (16 Refs)

13. ARGON LASER AND XENON ARC COAGULATION OF MALIGNANT CHOROIDAL MELANOMATA: HISTOLOGICAL FINDINGS IN SIX CASES.

Duvall J, Lucas DR
Dept. Opthalmology, Pathology, Univ. Manchester, Oxford Rd., Manchester M13 9PT, England
Br J Ophthalmol; 65(7):464-468 1981

Histological findings in six eyes with melanomata which had been treated by photocoagulation are reported. All cases had been treated with Argon laser, Xenon arc, or a combination of the two. Histological findings in 100 globes enucleated for malignant melanoma were also reviewed. The retina overlying the tumor was destroyed in all cases and Bruch's membrane was ruptured in 5 cases. The frequency of rupture of Bruch's membrane is greater in tumors treated by photocoagulation, as evidenced by the 100 untreated cases. Of these, 35 showed rupture of Bruch's membrane; of those only 4 were of low to intermediate malignancy. No difference was seen between cases treated with argon laser alone and those treated with a combination of argon laser alone and xenon arc. Three cases of mixed tumors ruptured Bruch's membrane and erupted into the vitreous, giving rise to reservation at the suggestion that cell type of the tumor is unimportant concerning the prognosis and effectiveness of photocoagulation. Lack of comment by previous author's on damage to Bruch's membrane appears to be due to treatment mainly by xenon arc; macular lesions are more likely to occur with argon laser. Necrosis in superficial parts of the tumor in globes enucleated shortly after treatment may be a direct effect of photocoagulation. There is no evidence of significant occlusion of the choroidal vessels adjacent to the tumor in any case. These results suggest that treating tumors which do not conform to specific criteria by photocoagulation is questionable due to resulting adverse effects. (27 Refs)

OTHER THERAPEUTIC MODALITIES

14. AROMATIC RETINOID IN THE TREATMENT OF MULTIPLE SUPERFICIAL BASAL CELL CARCINOMA, ARSENIC KERATOSIS AND KERATO-ACANTHOMA.

Berretti B, Grupper C, Edelson Y, Bermejo D
Dept. Dermatology, Polyclinique D'Aubervilliers, F-93300 Aubervilliers, France
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The aromatic retinoid Ro 10-9359 (Tigason; 1.0-1.5 mg/kg/day for 4-24 mo) was used to treat patients with: relapsing multiple basal cell carcinoma (BCC, 2), multiple BCC associated with arsenic intoxication (2), multiple BCC associated with multiple actinic keratosis (17), multiple actinic keratoses (12), keratoacanthomas (3). Complete clearing was obtained in 25 cases, no improvement in 4. Some side effects were recorded in 90% of patients, treatment had to be discontinued in some cases. Initial results were promising, but further work and longer follow-up are necessary. (5 Refs)

15. RETINOID AND SKIN CANCER PREVENTION.

Schnitzler L, Verret JL
Service de Dermatologie, F-49036 Angers Cedex, France
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The efficacy of aromatic retinoid (Ro 10-9359; etretinate) in preventing epithelial neoplasia was tested in human skin diseases with high risk of malignant transformation. Av dose was 0.5-1.0 mg/kg/day for 20-33 mo according to tolerance; the lower doses were given if side effects became marked. Patients selected had xeroderma pigmentosum (XP) with or without malignant tumors (4), Mibelli's porokeratosis (MPK) with multifocal cutaneous carcinoma (1), basal nevus syndrome (BCNS) with multiple basal cell carcinoma (1), familial epithelioma of Ferguson-Smith (1), and actinic keratosis (7). Apparent epitheliomas had been treated previously by surgery, electrocoagulation, or radiotherapy. Number of epitheliomas observed 3-4 yr before and during retinoid treatment (or in BCNS and one XP case treated vs an untreated sibling) was compared. Keratoses disappeared almost completely in XP cases; only one epithelioma was noted during 32 mo of treatment compared with multiple keratoses and epitheliomas registered previously. Treatment in these cases was ineffective against pigmentation abnormalities: lentigos (1 case) and Dubreuilh melanosis and malignant melanoma (1 case) were observed. In MPK retinoid was stopped after 2 yr; 3 mo later keratosis and Bowen's disease had developed. BCNS and Ferguson-Smith disease results were difficult to evaluate. With solar keratosis, regression was apparent from mo 2 of treatment; partial recurrence was seen 3 mo after stopping therapy. Preliminary results indicate the retinoid therapy may prevent or delay development of cutaneous carcinomas in some cutaneous diseases with risk of malignancy. (10 Refs)

16. RO 10-9359 IN EPIDERMODYSPLASIA VERRUCIFORMIS. PRELIMINARY REPORT.

Jablonska S, Obalek S, Wolska H, Jarzabek-Chorzelska M
Klinika Dermatologiczna A.M., Ul. Koszykowa 82a, 02-0088 Warszawa, Poland
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Ro 10-9359 (1 mg/kg/day; max dose 75 mg/day) was used successfully to treat three patients with epidermodysplasia verruciformis (EV) induced by oncogenic papilloma virus HPV-3 and one with EV induced by both HPV-3 and HPV-5. Great improvement was noticed in all patients; effect depended on dose. In one case a decrease in dose to 30 mg/day caused relapse. Mild to severe side effects were noted in all patients. (17 Refs)

17. UNORTHODOX METHODS IN TUMOR THERAPY: IS HYPERTHERMIA A WELL-FOUNDED METHOD?.

Streffer C
Institut fur Medizinische Strahlenphysik und Strahlenbiologie, Universitatsklinikum Essen, Hufelandstrasse 55, D-4300 Essen, W. Germany
MMW; 123(37):1368-1369 1981

The status and possibilities of hyperthermia in tumor therapy are discussed. Hyperthermia (42-45 C) leads to cell death, but there is no noteworthy difference in the heat sensitivity of normal and tumor cells, which makes local, selective hyperthermia of tumors necessary in tumor therapy. The effect of radiation therapy is considerably enhanced when followed immediately or within a few hr by hyperthermia. There is no method currently available for the selective hyperthermia of tumors. More than 3,000 patients were treated by hyperthermia, mostly combined with radiotherapy, in more than 60 trials during the period 1977-1980. Most tumors were the head and neck tumors, melanomas, and soft-tissue sarcomas. Complete tumor regression was seen very rarely after exclusive hyperthermia, but more frequently after hyperthermia combined with radiotherapy. Hyperthermia was favorable especially in the case of large tumors. Hyperthermia was also found useful in the palliative treatment of advanced cases, resulting in rapid tumor regression and alleviation of pain. A randomized multicenter trial with hyperthermia is in process in West Germany, and includes patients with non-small-cell bronchial carcinoma, and carcinoma of the hypopharynx, oropharynx , and larynx. (3 Refs) (In GER)

MULTIMODAL THERAPY

18. TREATMENT OF PARAPSORIASIS EN PLAQUES AND MYCOSIS FUNGOIDES WITH AN ORAL AROMATIC RETINOID (RO 10-9359).

Souteyrand P, Thivolet J, Fulton R
Clinique Dermatologique, Hopital E. Herriot, F-69374 Lyon Cedex 2, France
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The aromatic retinoid Ro 10-9359 (AR) was tested in 10 patients, including 3 with parapsoriasis en plaque (PPP), 6 with mycosis fungoides (MF), and 1 with Sezary's syndrome (SS). Three PPP and two MF patients received AR (1 mg/kg body wt/day for 1 mo and 0.7 mg/kg body wt/day thereafter) as sole treatment. Four MF and the 1 SS patient received AR (1 mg/kg body wt/day for the duration of treatment) in combination with psoralen-UV-A (PUVA) treatment. Among those receiving only AR two PPP patients showed clinical improvement; MF did not respond to AR treatment. Four MF patients who had had relapses after PUVA therapy showed complete clearing of lesions with combined AR and PUVA therapy. The SS patient showed improvement only on the palmo-plantar keratodermia. The mechanism by which AR produced results was not determined. (no Refs)

CASE REPORTS

19. LOCAL TREATMENT OF LENTIGO MALIGNA WITH AZELAIC ACID.

Ertle T, Wiskemann A, Janner M
Dept. Dermatology, Univ. Hamburg, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Arch Dermatol Res; 271(2):197-203 1981

Lesions of lentigo maligna in a patient suffering from xeroderma pigmentosum were treated for 3 mo with an ointment containing azelaic acid (C-9-dicarboxylic acid). No significant clinical improvement was noted. Histological alterations included epidermal hyperplasia and reduction in number and pigmentation of melanocytes. (7 Refs)

20. APOCRINE ADENOMA VERSUS APOCRINE CARCINOMA. REPORT OF 2 CASES (MEETING ABSTRACT).

Okun MR, Finn R, Blumental G
Department of Dermatology, Tufts University School of Medicine, Boston, MA
Zentralbl Haut Geschlechtskr; 145(4):313 1981

Report of 2 cases: 6 mm large tumor on the cheek of an 81 yr old man and a tumor of the same size on the cranium of a 57 yr old man. Histologically there were features of an apocrine adenoma along with those of an apocrine adenocarcinoma. Such tumors are often not recognized because of their rarity and their initially prolonged seemingly benign slow growth. The problem of their differentiated diagnosis is discussed. (no Refs) (In GER)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

21. EVIDENCE FOR LINKAGE BETWEEN HLA AND MALIGNANT MELANOMA.

Hawkins BR, Dawkins RL, Hockey A, Houliston JB, Kirk RL
Sch. Medical Technology, Western Australian Inst. Technology, Hayman Road 6102, Western Australia, Australia
Tissue Antigens Histocompat Immunogenet; 17(5):540-541 1981

A large kindred with multiple cases of malignant melanoma in which susceptibility to the disease is apparently inherited in an autosomal dominant manner and segregates with the human leukocyte antigen complex. In one part of the kindred susceptibility to the disease apparently segregated with haplotype A2, CW1, B27, DR2, and in another section with A24, CW3, BW55, DR(-0) suggesting a recombination distance of 10 units which is consistent with a recombination having occurred. (8 Refs)

22. KAPOSI'S SARCOMA. IV. DETECTION OF CMV DNA, CMV RNA AND CMNA IN TUMOR BIOPSIES.

Boldogh I, Beth E, Huang ES, Kyalwazi SK, Giraldo G
(c/o Huang) Cancer Res. Center, Univ. North Carolina, Chapel Hill, NC, 27514
Int J Cancer; 28(4):469-474 1981

In order to determine whether human cytomegalovirus-(CMV) DNA homologous sequences as well as CMV-specific RNA(s) and antigen(s) exist in tumor biopsies of Kaposi's sarcoma (KS) DNA-DNA reassociation, RNA-DNA in situ cytohybridization and anticomplement immunofluorescence test (ACIF) tests were applied. Three of 10 DNAs extracted from Kaposi sarcoma biopsies contained DNA sequences homologous to radioactively labeled human CMV DNA probe. The amount of CMV DNA in these sarcoma tissues was calculated to range from 0.7 to 1 genome equivalent per diploid cell. The presence of virus-specific RNA was also demonstrated in sections from 5 of 10 tumor biopsies. CMV-determined nuclear antigen(s) (CMNA) present in variable degrees were also demonstrated. In contrast, we could not detect any herpes simple virus type II (HSV-2) or Epstein-Barr virus (EBV) DNA sequences in DNA of these tumor biopsies. Furthermore, there were no detectable HSV-2 or EBV-specific RNA or virus-specific antigens in sections of these biopsies. These results provide new lines of evidence for the relationship between CMV and Kaposi's sarcoma. (Author abstract) (34 Refs)

23. BASAL CELL CARCINOMATOUS CHANGES ON THE LOWER LEG: AN ASSOCIATION WITH CHRONIC VENOUS STASIS (MEETING ABSTRACT).

Walkden V, Black MM
Department of Dermatology, St Thomas' Hospital, London SE1 7EH, England
Brit J Dermatol; 105(Suppl19):9 1981

Although malignant change in stasis ulcers is rare, the studies indicate that squamous cell carcinoma is the commonest neoplasm encountered. Our experience over a 15-yr period differed from this widely held view and showed that basal cell carcinoma occurred much more commonly than might have been expected. Our study consisted of nineteen cases (nine male and ten female), with an age range presentation of 48-88 yr (means 65.7 yr). Twelve had been treated for chronic 'stasis' ulcers, four had nodular basal cell carcinomas (BCC) on the lower leg, and in one, sections taken from 'normal' skin removed at the time of varicose vein surgery showed microscopic evidence of superficial, multifocal BCC. The duration of the ulcers or nodules was from six mo to twenty yr with a mean of 5.4 yr. Interestingly, nearly all the ulcers occurred at sites on the lower leg which would be considered somewhat atypical for a chronic stasis ulcer. There was a history of trauma at the site of the lesion in six cases, and marked superficial varicosities were also only obvious in further six. Excision and grafting was curative in those cases in whom it was performed. All the biopsies showed histological changes of moderate or marked venous stasis. The BCCs tended to be only slowly invasive and were characterized by a marked, stromal reaction and surrounding fibrosis. Skin adjacent to ulcers showed epidermal hyperplasia with marked elongation of rete ridges, some of which were the site of multifocal microscopic BCC transformation. (no Refs)

SELECTED PRECLINICAL STUDIES

24. THE USEFULNESS OF HUMAN TUMOR CELL LINES IN THE STUDY OF CHEMOSENSITIVITY. A STUDY OF MALIGNANT MELANOMAS.

Tveit KM, Fodstad O, Pihl A
Norsk Hydro's Inst. Cancer Res., Montebello, Oslo 3, Norway
Int J Cancer; 28(4):403-408 1981

The chemosensitivity of human melanoma cells has been studied before and after continuous in vitro culture. Altogether, nine cell lines were studied, two derived from patients' biopsies, and seven from xenografts in athymic mice. The sensitivity to the agents DTIC (Dacarbazine), CCNU (Lomustine), procarbazine, vinblastine, abrin and ricin was assayed. Furthermore, in five cases the chemosensitivity of the cell lines was compared to that of tumors obtained by injecting the cell lines into athymic mice. In all cases the sensitivity was measured in an in vitro soft agar assay. Upon cultivation in vitro, two of the cell lines, one derived from a patient's metastasis and one from a xenograft in athymic mice, showed marked increases in sensitivity to some of the drugs, whereas sensitivity to other drugs showed little or no change. For the other cell lines small, but definite increases or decreases in chemosensitivity were observed. Permanent cultures showed the same chemosensitivity as early subcultures. The tumors formed by injecting the cell lines into athymic mice showed moderate changes in chemosensitivity, as compared to the cell lines in vitro. The data indicate that considerable changes in chemosensitivity may occur when cells are brought from in vivo to in vitro conditions and vice versa and that such changes may be highly specific. Therefore, although cell lines may be useful in some respects, they should be used with caution in attempts to evaluate quantitatively the sensitivity of human tumors to cancerostatic drugs. (Author abstract) (25 Refs)

25. INHIBITORY EFFECTS OF AURANOFIN ON KB AND MELANOMA CELLS (MEETING ABSTRACT).

Simon TM, Kunishima DH, Lorber A
Memorial Hospital Medical Center of Long Beach, Long Beach, CA, 90801
In Vitro; 17(3):259 1981

Auranofin (AF) is a recently developed coordinated gold anti-rheumatic agent that we have previously reported to exert anti-tumor activity in the lymphocytic leukemia P388 animal tumor model and to inhibit in vitro proliferation HeLa and RAJI cells. Recent studies comprising this report assess the effect of AF utilizing in vitro drug screening tumor cell line KB and a human melanoma cell culture (MH28) established from a melanotic nodule. DNA, RNA, and protein synthesis were measured by macromolecular incorporation of 3H-thymidine, 3H-uridine, and 3H-leucine respectively. We observed AF at concentrations of 50-100 ug Au/dl to exert a concentration-dependent inhibition, greater than 50% of DNA, RNA, and protein synthesis in KB cells after exposure for 24 hr. Pretreatment for 6 hr at concentrations of 100 ug Au/dl resulted in irreversible inhibition of 3H-thymidine uptake. The MH28 cells were also observed to manifest significant inhibition of 3H-thymidine uptake and striking changes in cell morphology by scanning electron microscopy displaying pitting, blebbing, and cratering, thereby supporting the concept that AF may have potential as an anti-neoplastic agent. (no Refs)

26. MULTINUCLEATION AND INHIBITION OF CYTOKINESIS IN SUSPENDED CELLS: REVERSAL UPON REATTACHMENT TO A SUBSTRATE.

Ben-Ze'ev A, Raz A
Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel
Cell; 26(1):107-115 1981

Cell proliferation under nonadhesive conditions was examined in anchorage-dependent mouse fibroblasts (3T3 and 3T6), in epithelial monkey kidney cells (BSC-1) and in four B16 melanoma cell variants that exhibit distinct metastatic properties. Nonadhesive conditions established by suspension culture in methyl cellulose or by plating on poly(2-hydroxyethylmethacrylate)-coated plates cause multinucleation and inhibition of cytokinesis in all cell types. Formation of binucleated cells in suspended 3T3 cells continues for 24 hr until DNA synthesis is completely inhibited. Twenty percent of the cells become binucleated during this time. During a similar period in suspension culture over 60% of a synchronized epithelial cell culture (suspended 8 hr after the initiation of S phase) became binucleated. The melanoma cells that maintain a high level of metabolism while in suspension continued to develop into multinucleated cells. After 3 days in suspension, 50% of the melanoma cells have more than one nucleus. Since cell number during suspension culture remains constant, because of a block in cytokinesis, there is a remarkable increase in cell size in suspended melanoma cells. When replated on tissue culture plates, normal cell division res umes by an early extrusion of the extra nuclei in melanoma cells. The melanoma cell variants, although displaying different metastatic potential in vivo, behave similarly in suspension culture. 3T3 cells require 24 hr of replating before recovering DNA synthesis and initiating extrusion of the extra nucleus. The results suggest a differential sensitivity of cytokinesis and karyokinesis to cell-surface contact with the substrate. (Author abstract) (33 Refs)

27. IN VITRO CYTOTOXIC DRUG SENSITIVITY TESTING OF HUMAN TUMOUR XENOGRAFTS GROWN AS MULTICELLULAR TUMOUR SPHEROIDS (MEETING ABSTRACT).

Jones AC, Stratford IJ, Wilson PA, Peckham MJ
Institute of Cancer Research, Royal Marsden Hospital, Sutton, England
Br J Cancer; 43(5):725 1981

Using a sequential static-spinner culture system, an attempt has been made to initiate multicellular tumor spheroid formation from 13 different xenografted human tumors. All the tumors used had been established in immune-suppressed mice and were taken from the second passage onwards. The range of tumor examined includes melanomas, ovarian, bronchial and breast carcinomas and a teratoma. Data on the colony-forming ability in soft agar of cells obtained from disaggregated spheroids have been obtained in 3 tumors. There appears to be a marked enhancement of the colony-forming ability of these cells, compared with the cells obtained directly by disaggregation of the tumor from the mouse. Individually growing spheroids obtained from 4 different tumors have a range of vol-doubling x of 2.4-15 days. Cytotoxic drug testing measurements of growth delay and clonogenic survival have been obtained with spheroids from a bronchial and a breast carcinoma. These results support the idea that multicellular tumor spheroids may be useful as a solid-tumor model in vitro, suitable for testing cytotoxic drug sensitivity. (no Refs)

28. RELEASE OF AN AUTOSTIMULATORY GROWTH ACTIVITY BY HUMAN MALIGNANT MELANOMA CELLS (MEETING ABSTRACT).

Richmond A, Lawson DH, Nixon DW
Department of Medicine, Emory University School of Medicine, Atlanta, GA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

We examined concentrates of Hs0294 conditioned medium (CM) and acid-ethanol extracts of this conditioned medium (CMae) for ability to stimulate (3H)-thymidine incorporation and increase cell number in other Hs0294 cultures. When 8-32 ug of CM protein was tested for ability to stimulate (3H)-thymidine incorporation, the minimal effective dose (MED) was 16 ug and higher concentrations of this preparation did not increase the stimulatory effect. Daily addition of 25 ug of CM protein to serum-free cultures increased cell number 40% above that of control cultures after four days of treatment. This same concentra tion of CM elevated (3H)-thymidine incorporation 71% above that of control. The MED for this preparation was 5.5 ug, with 11 ug producing a half-maximal response and 22 ug producing the maximal response. Twenty-four ug of CMae stimulated the incorporation of (3H)-thymidine into DNA to 100% greater than control and increased cell number to 55% greater than control. Although CMae from early passage primary cultures of a non-malignant nevus did not contain melanoma growth stimulatory activity (MGSA), these cells did respond to this substance. The activity is stable to IN acetic acid at 25C for 48 hr and stable to boiling for 10 min. Acid-ethanol extracts of 5 human melanoma tumors also contained MGSA, as determined by ability to stimulate (3H)-thymidine incorporation in Hs0294 cells. The MED of these tumor extracts ranged from 1-10 μg, producing maximal stimulation of (3H)-thymidine incorporation 51-130% greater than control. Thus, MGSA may contribute to the proliferation of tumor cells in vivo and in vitro. (no Refs)

29. EXPRESSION OF TUMOR-ASSOCIATED ANTIGENS AND KINETIC PROFILE OF TWO IN VITRO HUMAN MELANOMA CELL LINES.

Badaracco G, Corsi A, Maisto A, Natali PG, Starace G, Zupi G
Istituto Regina Elena per lo Studio e la Cura dei Tumori, Rome, Italy
Cytometry; 2(2):63-69 1981

The growth characteristics and the antigenic profile of established human melanoma cell lines M10 and M14 are reported. While growth curves in culture, studied by flow cytometry, were fairly typical, there were some unusual features which were confirmed by their DNA distribution content. In the late stages of growth the cell DNA content resumes the initial distribution, suggestive of partial recovery of cell proliferating potential. Reactivity of three monoclonal antibodies (MoAb) to human melanoma associated antigens was assessed in normal and transformed melanocytes by indirect immunofluorescence (IIF). Staining of M10 and M14 lines with the three MoAb 225, 465 and Q5/13 showed that expression of melanoma-associated antigens as detected by IIF on the plasma membranes did not exhibit appreciable variations during the different growth phases studied during 4-13 days of culture. (9 Refs)

30. IN VIVO MODELS FOR STUDIES OF HUMAN TUMOR METASTASIS (MEETING ABSTRACT).

Hanna N
Cancer Metastases and Treatment Laboratory, Frederick Cancer Research Center, Frederick, MD, 21701
Chesapeake Conference on Hemostasis and Malignancy-Interaction of Platelets and Tumor Cells, June 26-30, 1981, St Mary's Maryland American Red Cross; 1981

The nude mouse has been the host of choice for studies of growth and metastasis of human tumors. Unfortunately, most malignant neoplasms that grew upon transplantation to nude mice failed to metastasize. We recently demonstrated that this natural resistance of nude mice to dissemination of allogeneic and xenogeneic tumors is mediated to a great extent by natural killer (NK) cells. Thus, young nude mice with low NK activity exhibit high incidence of pulmonary metastases following iv injection of allogeneic and xenogeneic metastatic tumors. The injection of a human melanoma cell line (A-375) into young nude mice resulted in the development and significant numbers of lung tumor colonies. Cell lines established from individual A-375 metastatic foci produced 20-100 x more pulmonary metastases than the parent cells following reinjection into young nude mice. The cellular properties of these highly metastatic melanoma cells (eg production of specific antigens, ability to aggregate platelets, and sensitivity to cytotoxic drugs, lectin-mediated cytotoxicity and to NK cell-mediated killing) are being studied in vivo and in vitro. (no Refs)

31. TUMOR CELL INTERACTIONS WITH VASCULAR ENDOTHELIAL CELLS AND THEIR EXTRACELLULAR MATRIX (MEETING ABSTRACT).

Nicolson GL, Kramer RH
Department of Oral Medicine, University of San Francisco, San Francisco, CA, 94143
Chesapeake Conference on Hemostasis and Malignancy-Interaction of Platelets and Tumor Cells, June 26-30, 1981, St Mary's Maryland American Red Cross; 1981

In order for distant blood-borne metastasis to form, circulating malignant cells must bind to the vascular endothelium and invade the underlying basement membrane. A model for this process has been developed using cultured vascular endothelial cell monolayers which synthesize a basolateral extracellular matrix or basal lamina. Metastatic tumor cells, as well as some normal cells such as WBC bind to vascular endothelial monolayers and stimulate endothelial cell retraction, exposure of the underlying extracellular matrix, migration of the malignant cells to the matrix surface and finally the destruction of the matrix. The movement of metastatic tumor cells to endothelial extracellular matrix appears to be due to an adhesive difference between the endothelial cell and the matrix surface. Human and murine melanoma cells adhere much more rapidly to the extracellular matrix, and this can be mimicked by the attachment of tumor cells to polyvinyl-immobilized fibronectin. Antifibronectin inhibits slightly binding of melanoma cells to matrix, but completely blocks binding to immobilized-fibronectin suggesting that this molecule may mediate only in part the enhanced adhesion of melanoma cells to matrix. Tunicamycin inhibits glycosylation of melanoma cell glycoproteins and blocks tumor cell-endothelial cell attachment in vitro and blocks experimental metastasis in in vivo. Metastatic cells release degradative enzymes which are capable of solubilizing the major components of the endothelial extracellular matrix: glycoproteins such as fibronectin and lamanin, collagens and sulfated proteoglycans. Tumor cells that lack these enzymes may not be effective in escaping the vascular compartment. (3 Refs)

32. GROWTH INHIBITION BY DEXAMETHASONE IN CLONAL VARIANTS OF HAMSTER MELANOMA CELLS: CHARACTERIZATION OF BIOLOGICAL RESPONSE AND ROLE OF MEDIUM COMPONENTS (MEETING ABSTRACT).

Buzard RL, Horn D
Molecular Biology Division, University of Southern California, Los Angeles, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Dexamethasone (10 nM) inhibits the growth, alters the morphology and decreases the final cell density in RPMI 3460 Syrian hamster melanoma cells. We have isolated clonal variants of RPMI 3460, one of which (clone 6) exhibits the same three biological responses to dexamethasone (DM) the parental cell line. The other clone (clone 5), while exhibiting the decrease in final cell density, fails to exhibit the growth inhibition and morphological alterations. Since progesterone antagonizes the biological responses of clone 5 and clone 6 cells to DM, it appears that all the responses are mediated by glucocorticoid receptors. Experiments in which DM is added to or removed from logarithmically growing clone 6 cultures indicate that growth inhibition can be induced or reversed in less than 24 hr after DM addition or removal. Moreover, DM which is added during early or mid-logarithmic growth is able to evoke the decrease in final cell density and DM which is removed during early or mid-logarithmic growth has no effect on final cell density in clone 5 and clone 6 cultures. Interactions of DM with factors in fetal calf serum are unnecessary for DM action in logarithmically growing clone 6 cells. Moreover, these factors must not be involved in the different responses of clone 5 and clone 6 cells to DM. Studies with conditioned medium suggest that the different phenotypes of clone 5 compared to clone 6 cells are not due to differences in the ability of the two cell lines to alter the medium by producing extracellular resistance or sensitivity factors, either in the presence or absence of DM. (no Refs)

33. NEW CLASS OF TRANSFORMING GROWTH FACTORS POTENTIATED BY EPIDERMAL GROWTH FACTOR: ISOLATION FROM NON-NEOPLASTIC TISSUES.

Roberts AB, Anzano MA, Lamb LC, Smith JM, Sporn MB
Lab. Chemoprevention, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 78(9,part2):5339-5343 1981

Proteins potentiated by epidermal growth factor (EGF) to induce a transformed phenotype in non-neoplastic rat kidney fibroblasts in cell culture have been isolated from many non-neoplastic tissues of the adult mouse, including submaxillary gland, kidney, liver, muscle, heart, and brain. They resemble previously described transforming growth factors (TGFs) isolated from neoplastic cells as follows: they are extractable by acid/ethanol and are acid-stable, low mol wt (6,000-10,000) polypeptides requiring disulfide bonds for activity, and they cause anchorage-independent growth of non-neoplastic indicator cells that will not grow in soft agar in their absence. Partial purification of these TGFs from submaxillary glands of male mice shows that they are distinct from EGF. Unlike previously described extracellular TGFs, but like certain cellular TGFs from neoplastic cells, they are potentiated by EGF in their ability to promote anchorage-independent growth. The isoelectric point of the submaxillary gland TGF protein is near neutrality. Chromatography on Bio-Gel P-30 followed by high-pressure liquid chromatography has resulted in a 22,000-fold overall purification. The most purified protein is active in inducing growth in soft agar in 1 ng/ml when assayed in the presence of EGF. The data add further evidence to the concept that neoplasia may result from a quantitative, rather than qualitative, alteration in non-neoplastic biochemical processes. (Author abstract) (25 Refs)

34. ENHANCEMENT OF CALCIUM UPTAKE AND PHOSPHATIDYLINOSITOL TURNOVER BY EPIDERMAL GROWTH FACTOR IN A-431 CELLS.

Sawyer ST, Cohen S
Dept. Biochemistry, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Biochemistry; 20(21):6280-6286 1981

Epidermal growth factor (EGF) stimulates the incorporation of 32Pi and [3H]inositol into phosphatidylinositol (5-10-fold) in A-431 cells. EGF also stimulates the incorporation of 32Pi into phosphatidic acid (up to 10-fold). These effects are attributed to an acceleration of the turnover of phosphatidylinositol as a consequence of the binding of EGF to its membrane receptor. The extent of the phosphatidylinositol response to EGF parallels the extent of hormone binding. The phosphatidylinositol response to EGF appears to be dependent on an influx of calcium since (1) external calcium is required for the enhancement of phosphatidylinositol turnover, (2) the accumulation of 45Ca by A-431 cells is stimulated by EGF, (3) blockage of calcium influx with LaCl3 inhibits stimulation of phosphatidylinositol turnover, and (4) calcium influx via ionophore A23187 is sufficient to stimulate phosphatidylinositol turnover. Since the binding, internalization, and degradation of 125I-labeled EGF in A-431 cells are unaffected by the omission of calcium from the medium, external calcium and phosphatidylinositol turnover are not necessary for the internalization and degradation of the EGF-receptor complex. (Author abstract) (31 Refs)

35. EFFECT OF EPIDERMAL GROWTH FACTOR ON PROLIFERATION OF HUMAN TUMOR CELLS IN SOFT AGAR.

Hamburger AW, White CP, Brown RW
Cell Culture Dept., Americn Type Culture Collection, 12301 Parklawn Drive, Rockville, MD, 20852
JNCI; 67(4):825-830 1981

The effect of epidermal growth factor (EGF) and fibroblast feeder layers on the proliferation of human tumor cells in soft agar was examined. The addition of EGF to medium supporting growth of tumor cells significantly increased (p less than or equal to 0.02) the number of colonies grown from the cells of 36 of 58 patients (62%) with a variety of neoplasms. The increase in the number of colonies was dependent on the concentration of EGF and was max at a concentration of 50 ng EGF/ml. The addition of glucocorticoids did not potentiate the effect of EGF. Lethally irradiated fibroblast feeder layers alone only slightly increased the number of colonies. However, the addition of fibroblasts to cultures significantly increased the mitogenic effect of EGF. The results suggest that a proportion of epithelial-derived tumors retain responsiveness in vitro to physiologic growth regulators such as EGF. (Author abstract) (28 Refs)

36. INDUCTION OF PLASMINOGEN ACTIVATOR BY UV LIGHT IN NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS.

Miskin R, Ben-Ishai R
Dept. Biochemistry, Weizmann Inst. Science, Rehovot, Israel
Proc Natl Acad Sci USA; 78(10):6236-6240 1981

Normal and DNA repair-deficient human fibroblasts have been used to study induction of plasminogen activator (PA) by DNA damage. UV light induced the synthesis of PA in skin fibroblasts of all types of xeroderma pigmentosum (XP) in XP heterozygotes and in human amniotic cells. Enzyme induction was, however, not observed in fibroblasts of normal adults. In classical XP, which are deficient in excision repair, PA synthesis occurred in a narrow range of low-UV fluences. In such strains, the level of enzyme produced was correlated with the extent of repair deficiency. UV fluences required for PA induction in XP variants and XP heterozygotes were at least 10x those inducing enzyme synthesis in excision-deficient XP. Max enzyme induction occurred 48 hr after irradiation, and the highest levels of enzyme produced were 15-20x those of PA baseline levels. Electrophoretic analysis showed that UV irradiation enhances the synthesis of the Mr 60,000 human urokinase-type PA, which is present in low amounts in untreated cells. Our results suggest that PA induction in human cells is caused by unrepaired DNA damage and represents a eukaryotic SOS-like function. In addition, PA induction may provide a sensitive assay for detection of cellular DNA repair deficiencies and identification of XP heterozygotes. (Author abstract) (42 Refs)

37. CHARACTERIZATION OF SURFACE MARKERS AND CYTOPLASMIC ORGANELLES IN BENIGN AND MALIGNANT LYMPHOID LESIONS OF SKIN; IMMUNOHISTOCHEMICAL AND ELECTRON MICROSCOPIC EVALUATION.

Jimbow K, Katoh M, Nishio C, Jimbow M
Dept. Dermatology, Sapporo Medical Coll., Minami 1, Nishi 6, Sapporo 060, Japan

J Cutan Pathol; 8(4):283-298 1981

In order to characterize the benign and malignant proliferation of lymphoid cells in skin, we compared surface markers and cytoplasmic organelles of cells in cutaneous lymphoid hyperplasia (CLH), lymphomatoid papulosis (LP), mycosis fungoides (MF), Sezary's syndrome (SS) and primary cutaneous malignant lymphoma (ML). The immunohistochemical study showed cells with both T- and B-cell markers in CLH, LP and early MF, whereas cells with only the T-cell marker were seen in late MF, SS and ML. T-cells in all cutaneous lesions possessed the surface marker common to T-cells of peripheral lymph nodes, and not that of central thymus cells. Cutaneous T-cells contained clustered or scattered dense core granules. Although no specific organelles indicative of benign or malignant lymphoid proliferation were found, there were several ultrastructural features that could help identify each form of cutaneous lymphoid lesions. These included clustered or scattered dense-core granules, the variable degree of nuclear convolutions as well as dendritic arborization, and the presence or absence of 10 nm filaments. (Author abstract) (18 Refs)

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DIAGNOSIS

1. HISTOLOGICAL AND CYTOLOGICAL CRITERIA IN THE DIAGNOSIS OF MALIGNANT MELANOMAS BY CRYOSTAT SECTIONS.

Braun-Falco O, Korting HC, Konz B
(c/o Korting) Dept. Dermatology, Univ. Hosp. Munich, Frauenlobstr. 9-11, D-8000 Munchen, W. Germany
Virchows Arch [Pathol Anat]; 393(1):115-121 1981

Although cryostat sections in general allow a distinction to be made between malignant melanomas and other pigmented lesions in clinically doubtful cases, the differential diagnosis may be difficult. The histological and cytological criteria taken into account can be classified as major, minor, and insufficient. Knowing the diagnostic value of each makes a conventionally established diagnosis safer. Variance analysis does not contribute to the problem but it can nevertheless be shown that the evaluation of six major criteria makes a quick and reliable

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cryostat section diagnosis possible. If these results are confirmed in a prospective study it would be a decisive step on the way to a quicker and safer cryostat section diagnosis of malignant melanoma, even for the less experienced histopathologist. (Author abstract) (9 Refs)

2. INCIDENCE OF METASTASES FROM MALIGNANT MELANOMA RELATED TO THEIR LOCATIONS AND THICKNESS (MEETING ABSTRACT).

Boeryd B, Eldh J, Peterson LE
Dept. of Pathology, University of Linkoping, Linkoping, Sweden
W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

The 277 patients treated during 1959-1973 for malignant melanoma with wide excision but with regular lymph node left intact, were followed up every 3 mo for the first three yr and then every 6 mo for up to 10 yr. As soon as regular lymph node metastases were diagnosed clinically they were excised except for 4 patients, who at the same time had dissemination to distant organs. The observation periods were at least 5 yr. Of the 48 patients who primarily developed lymph node metastases, 30 died later of disseminated metastases. Another 30 patients died of metastases, primarily to distant organs. The av time for excision of lymph node metastases from melanomas in all locations except for the trunk was similar, and so was the av time for death. Lymph node metastases from melanomas of the trunk appeared later and the patients survived longer. The thickness of the tumors did not obviously influence these parameters. On the contrary, primarily distant metastases from melanomas on the feet were diagnosed earlier than from melanomas on other locations, but there was no big difference in the av time for death irrespective of location. However, melanomas thicker than 3 mm metastasized much earlier to distant organs and killed the patients earlier than did thinner melanomas. (no Refs)

3. SKIN IMPRINT CYTOLOGY IN THE DIAGNOSIS OF CUTANEOUS T-CELL LYMPHOMAS (MEETING ABSTRACT).

Rosen SE, Koprowska I, Vonderheid EC
Department of Pathology, Temple University Hospital, Philadelphia, PA
Twenty-ninth Annual Scientific Meeting of the American Society of Cytology, November 2-7, 1981, St. Louis, Missouri. The Society 90 pp., 1981.

The early diagnosis of cutaneous T-cell lymphomas (CTCL) is difficult. Diagnostic criteria for early skin and lymph node involvement are not well defined, and recognition of the abnormal cerebriform lymphocte, while diagnostically helpful, may be difficult in tissue sections. A study of touch imprint cytology in the diagnosis of CTCL was begun with the following aims: 1) to evaluate the accuracy of the imprint technique: 2) to better characterize cytologic findings in early and late lesions of CTCL; and 3) as a long-term goal, to improve cytologic criteria for the early diagnosis of CTCL. This is a preliminary report of the study. Touch imprints were made on nine skin biopsies and two lymph nodes in which there was clinical suspicion of CTCL. Specimens were fixed in alcohol and stained by the Papanicolaou technique. Imprints from a variety of inflammatory dermatoses were used as controls. Cytologic and histologic interpretations were compared. The cytologic diagnosis was positive for mycosis fungoides (MF) in two cases suggestive of MF in four, and negative in three cases. These results correlated with the histologic diagnoses. Skin imprints from cases diagnosed as MF showed moderate to marked cellularity with a preponderance of lymphocytic cells and rare cerebriform cells. Skin imprint cytology appeared to be a reliable method in the diagnosis of CTCL in these cases. Cellular morphology and ability to identify cerebriform cells was enhanced by the Papanicolaou technique. (no Refs)

4. CLINICAL AND HISTOLOGICAL STUDIES OF THE CLASSIFICATION AND THE NATURAL COURSE OF THE STRAWBERRY MARK.

Nakayama H
Dept. Dermatology, Tokyo Metropolitan Bokutoh Hosp., 23-15, Kohtobbashi 4-chome, Sumida-ku, Tokyo 130, Japan
J Dermatol (Tokyo); 8(4):277-291 1981

A clinical classification is proposed for strawberry mark, the hemangioma common among infants. The natural course of each clinical type has been examined. Of 1247 new cases seen during a 16 yr period, 1046 were single lesions and 201 were multiple; 356 patients were male and 891 female. Natural course was followed in 255 cases having 308 lesions for 3-13 yr. Anatomic distribution is presented; the lesions were classified as common or giant lesions and divided into three major types: plaque (99 cases; lesions showing two-dimensional extension without elevation or elevation up to 3 mm), tumor (189 cases; lesions forming tumors as a result of dimensional growth, with three subtypes for main component id, dermal and sc components both conspicuous, or main component sc and slight dermal component), and sc (20 cases; lesions seated exclusively in the sc tissue). Spontaneous regression occurred more quickly among plaque and sc lesions (common lesion resolution by 5 and 7 yr, respectively) than in the tumor type (approx 40% cure by 10 yr). Prognosis of a lesion could be predicted once the clinical type was known. Clinical features of residual lesions included telangiectasia, skin redundancy with wrinkles, and protuberance. Histological examination of 65 lesions in 62 patients showed hyaline degeneration in capillary walls. Theories for the mechanism of regression are reviewed. (25 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

5. HUMORAL IMMUNE RESPONSE IN MELANOMA AND GLIOMA PATIENTS: A SOLUBILIZED MELANOMA-MEMBRANE COMPONENT AS A TOOL FOR DETECTING CIRCULATING ANTIBODIES.

Birkmayer GD
Institut fur Zellbiologie, Goethestrasse 33, D-8000 Munchen 2, W. Germany
Cancer; 48(11):2399-2408 1981

In search of tumor-associated components in human melanomas and gliomas, plasma membranes were isolated from these tumors and compared morphologically, biochemically and immunologically with those from normal human brain. The preparations exhibited a comparable ultrastructure of empty vesicles of various form and size. The melanoma membrane consisted of at least 15 protein components and the glioma membrane consisted of at least 24 protein components, 4 of which were absent in the membrane of normal tissue, as revealed by polyacrylamide gel electrophoresis. The four tumor-associated polypeptides could be solubilized together with a few other membrane components by the non-ionic detergent Triton-X100 and were used as an antigen source for immunologic character-

HE 20.3173/2:

ization of melanoma and glioma membranes. A rabbit antiserum prepared against these solubilized membrane components from melanoma and glioma membranes. A rabbit antiserum prepared against these solubilized membrane components from melanoma was absorbed with plasma membranes from a variety of normal tissue including RBC, lymphocytes, spleen, liver, lung, kidney, placenta and brain. The absorbed antiserum reacted with the membrane extract of all the 11 melanomas tested so far; in addition it crossreacted with an identically prepared extract from all the 15 gliomas tested. Membrane extracts from other tumors, such as kidney and mammary carcinoma, were negative in this respect. Furthermore, a rabbit antiserum prepared against the Triton extract from glioma membranes yielded after exhaustive absorption an immune precipitate not only with the specimens from the 15 other gliomas but also with those from the 11 melanomas. Electrophoretic analysis of the immune precipitate formed by the Ig fraction of the absorbed rabbit antiserum and the Triton-X100 extract from melanoma membranes exhibited six polypeptide bands, two of which appear antigen-derived as they were missing in the profile of the Ig pattern. A comparable electrophoretic pattern was obtained with the immune precipitate of the glioma antigen specimen. The mol wt of these two polypeptide was estimated on the basis of their electrophoretic mobility to be [illegible]00 and 10,000 daltons, respectively. The electrophoretic immunologic findings argue for a common membrane component in human melanoma and glioma patients. Using the Triton extract from melanoma membranes as an antigen source, precipitating antibodies could be detected in the Ig fraction of 16 of the 24 sera from melanoma patients and in that of 15 of the 23 glioma patients by means of counter-current electrophoresis. Sera from a variety of cancer patients with diseases other than melanoma or glioma as well as from patients without cancer w ere negative in this respect. (Author abstract) (37 Refs)

6. ADJUVANT REACTIVITY PREDICTS SURVIVAL IN PATIENTS WITH HIGH-RISK PRIMARY MALIGNANT MELANOMA TREATED WITH SYSTEMIC BCG.

Cochran AJ, Buyse ME, Lejeune FJ, Macher E, Revuz J, Rumke P
(c/o Lejeune) Dept. Surgery, Inst. Jules Bordet, Centre des Tumeurs de l'Universite Libre Bruxelles, 1000 Brussels, Belgium
Int J Cancer; 28(5):543-550 1981

We report the prognostic importance of strength of reaction to BCG, tumor histology and clinical factors in patients with previously untreated high-risk (Clark, III, IV and V) primary malignant melanoma. One hundred and one such patients received high-dose BCG (1 x 10(8) viable units) by Heaf gun as an adjuvant to standardized primary surgery according to EORTC Protocol 18741. Univariate analysis of disease-free interval (DF) indicates that the degree of max reaction to BCG ($p = 0.0003$), Breslow thickness ($p = 0.0003$) and Clark level ($p = 0.002$) are highly significant prognostic factors. When a multivariate model using Cox's proportional hazard regression was used for DFI, the degree of max reaction to BCG and Breslow thickness were by far the most significant criteria. A prognostic equation was obtained to predict DFI from max BCG reaction and Breslow thickness. From analysis of the scores calculated in this way it appears that the two variables act independently. This technique permits the determination of values that are predictive of DFI and discriminate between subgroups of patients with different DFI characteristics (5 groups, p less than 0.0001). This exercise was repeated for survival and similar results were obtained. The degree of a patient's immune reaction to BCG administered therapeutically is of paramount importance in determining the likelihood of survival. This factor and the Breslow thickness can be integrated to produce a mathematical equation which accurately predicts survival for appropriately treated melanoma patients. (Author abstract) (25 Refs)

7. T LYMPHOCYTE SUBSETS IN PATIENTS WITH MALIGNANT MELANOMA.

Karavodin LM, Giuliano AE, Golub SH
Div Oncology, Dept. Surgery, UCLA Sch. Medicine, Los Angeles, CA, 90024
Cancer Immunol Immunother; 11(4):251-254 1981

The value of T lymphocyte subset profiles as an indicator of disease progression in malignant melanoma (MM) was studied. Cryopreserved lymphocytes from 57 MM patients and 19 normal individuals were assayed. Monoclonal antibodies were used to identify lymphocyte populations: OKT3.PAN for total peripheral T cells, OKT4.IND for inducer-helper subclass, and OKT8.SUP for suppressor-cytotoxic subclass. Analysis of subset profiles indicated no correlation between any of the subset values and presence or absence of disease, stage of disease, clinical outcome, age, or sex of the patients. A sequential study of th ree patients with recurrent disease showed no predictable variation of values during the course of the disease. Results indicate no systemic imbalance among T cell subsets in MM. More localized T cell imbalance, such as in lymph nodes adjacent to the tumor, is suggested as a possibility. (19 Refs)

8. RELATIONSHIP BETWEEN NATURAL KILLER CELL ACTIVITY AND HISTOLOGICAL FEATURES OF LYMPHOCYTE INFILTRATION AND PARTIAL REGRESSION OF THE PRIMARY TUMOR IN MELANOMA PATIENTS.

Hersey P, Hobbs A, Edwards A, McCarthy WH, McGovern VJ
Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, New South Wales 2000, Australia
Cancer Res; 42(1):363-368 1982

A group of 194 melanoma patients with Stage I melanoma was studied in an attempt to correlate histological features of prognostic importance in malignant melanoma with the level of natural killer cell (NK) activity in blood mononuclear cells. Histological features examined were lymphocytic infiltrate of the tumor base, lymphocyte infiltration at the tumor margin, and evidence of partial regression in the tumor. NK activity against melanoma cells and non-melanoma cells was studied in the same patients before and after surgical removal of melanoma. Patients with high NK activity against melanoma and Chang cells had less lymphocyte infiltrate at the base of the tumor irrespective of its thickness than did those with low NK activity. Patients with low NK activity and thin tumors had more lymphocyte infiltration at the base of the tumor than did those with high NK activity. Similar results were obtained in certain subsets of cases with respect to lymphocytic infiltration at the tumor margins and to the presence of partial regression. Although the nature of the association between these histological features and NK activity in blood is unknown, it is suggested that previously unexplained associations between histological features and prognosis may be accounted for by their association with NK activity. If this proves to be correct, measurement of NK activity may be an important additional prognostic factor in patients with melanoma. (Author abstract) (23 Refs)

9. AUTOIMMUNIZATION IN PATIENTS WITH MALIGNANT MELANOMA (MEETING ABSTRACT).

Sutherland CM, Krementz ET
Tulane University School of Medicine, New Orleans, LA
W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

Specific active immunotherapy has been studied in patients with malignant melanoma. Fourteen patients with Stage II or Stage III melanoma who could have all of their gross diseases resected and on whom a tissue culture cell line could be established were treated. Autologous tumor cells were harvested, irradiated, mixed with BCG, and administered at two-wk intervals. Between 8 x 10(6) to 58.9 x 10(6) cells were given. Immune response was measured by fluorescent antibody production and by in vitro cytotoxicity. The median disease-free interval was 9.5 mo, the median survival was 23 mo; there was 36% four-yr survival and 29% five-yr survival. The longest survival occurred in patients who developed high titers of antibody. Of those patients who subsequently relapsed, there was a 27% complete remission rate when subsequently treated with chemotherapy. Again, response to chemotherapy correlated well to antibody production. It appears that specific active immunotherapy with tissue cultured autologous tumor cells is a promising method of treatment for malignant melanoma. (no Refs)

10. IMMUNOPHARMACOLOGICAL AND CLINICAL INVESTIGATIONS WITH AN IMMUNOMODULATOR - OK-432-IN PATIENTS WITH MALIGNANT MELANOMA (MEETING ABSTRACT).

Micksche M, Kokoschka EM, Knobler A, Uchida A
Institute for Cancer Research, Vienna University, Vienna, Austria
W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

OK-432, a streptococcal preparation developed in Japan has been recently demonstrated to be a potent immune response modifier. We investigated the therapeutic and immunomodulating properties of this preparation in patients with malignant melanoma. Altogether, 35 patients (12 single doses, on application by one route, 15 frequent applications by one route, 7 combined routes) received OK-432 id, im, intrapleurally, ip, iv, respectively. Therapy was well tolerated (side effects noted were fever and chills in patients, especially after iv and intracavitary applications). Clinical outcome of 22 evaluable patients can be considered favorable, in 14 of them. Immunopharmacological studies revealed that iv, id and im route of OK-432 is able to enhance significantly natural killer (NK)-cell activity (4 hr Cr release assay, K 562 target) in treated melanoma patients. Furhter studies showed that it is possible to activate NK-cell activity in vitro by preincubation of patients' lymphocytes with OK-432, cytotoxicity was comparable with that after addition of interferon. Both in vivo and in vitro studies clearly demonstrate that OK-432 is a potent immunomodulator, and, furthermore, there is some evidence for a therapeutic benefit for melanoma patients treated with OK-432 for a longer period of time. (no Refs)

11. IMMUNE COMPLEXES IN SERA FROM MELANOMA PATIENTS (MEETING ABSTRACT).

Olberding P, Koldovsky P, Goerz G, Merk H
Institute of Environmental Hygiene, University of Dusseldorf, Dusseldorf, W. Germany
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Under normal conditions the immune complexes are removed from the peripheral blo od almost as fast as they are formed. The Raji-assay was used for detection of the complexes. Presence of the complexes adhering to Raji cells can be demonstrated by binding radiolabeled Protein A. In various groups of control persons, all 55 yr old, the complexes were found in 4%-9%. However the sera of melanoma patients were positive in more than 70%. The presence and amount of complexes reflects to a certain degree the clinical status of the patients. The presence of a large amount of complexes is a poor prognostic sign. After a successful operative removing of the tumor, the complexes usually disappear. (no Refs)

12. SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS.

Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeld SJ, Gold J, Hassett J, Hirschman SZ, Cunningham-Rundles C, Adelsberg BR, Parham DM, Siegel M, Cunningham-Rundles S, Armstrong D
Mt. Sinai Medical Center, New York, NY, 10029
N Engl J Med; 305(24):1439-1444 1981

Cellular immunodeficiency associated with chronic perianal ulcerative herpes simplex lesions is reported in four homosexual men. Onset of the disease was characterized by malaise, fever, and wt loss. Later infections included cytomegalovirus, Pneumocystis carinii, and Candida albicans. One patient developed Kaposi's sarcoma. Skin anergy, lymphopenia, poor or absent responses to plant lectins and antigens in vitro, and depressed natural killer cell activity against target cells infected with herpes simplex virus were observed. An association may exist between primary cytomegalovirus infection and a particularly prolonged cellular immunodeficiency state. (29 Refs)

13. IMMUNOCHEMICAL AND IMMUNOCYTOCHEMICAL LOCALIZATION OF S-100 ANTIGEN IN NORMAL HUMAN SKIN.

Cocchia D, Michetti F, Donato R
Dept. Anatomy, Universita Cattolica, Roma 00168, Italy
Nature; 293(5836):85-87 1981

The presence of S-100 antigen in normal human skin is reported. Levels of S-100 were measured by microcomplement fixation assay in normal skin and in human melanomas using a specific antibody raised against ox S-100. The amounts of S-100 were measured in samples containing 15 or 25 ug total protein; no appreciable anticomplementary activity was observed. The S-100 antigen was detected in measurable amounts in both the normal skin (0.03 ug/mg soluble protein) and melanoma (1.90 ug/mg soluble protein). In normal epidermis, S-100 reaction product was detected by electron microscopy (using the unlabelled antibody Papanicolaous's test with the same antiserum) in the perikarya and in the cytoplasmic processes of both melanocytes and Langerhans cells. No reaction production was present in the keratinocytes of any epidermal layer. In normal dermis, S-100 reaction product was detected not only in typical Langerhans cells , but also in cells with ultrastructural features comparable with Langerhans cells but lacking the characteristic granules. The results indicate that definite cutaneous cell types normally contain significant amounts of S-100 antigen, but at a much lower concentration than in malignant tissue. (22 Refs)

CHEMOTHERAPY

14. HIGH-DOSE NITROGEN MUSTARD (HN2) WITH AUTOLOGOUS NONFROZEN BONE MARROW TRANSPLANTATION IN ADVANCED MALIGNANT MELANOMA: A PHASE I TRIAL.

Hartmann DW, Robinson WA, Morton NJ, Mangalik A, Glode LM
(c/o Robinson) Dept. Medicine, Diy. Medical Oncology, Univ. Colorado Health Sciences Center, 4200 East Ninth Ave., Denver, CO, 80262
Blut; 42(4):209-220 1981

Three patients with advanced malignant melanoma (MM) were treated with high-dose (33 mg/square meter) nitrogen mustard (HN2) followed by autologous bone marrow transplants. Two patients had measurable disease at the time of treatment. Bone marrow (1.1-5.5 x 10(5) committed stem cells/kg body wt) was reinfused 48 hr after bolus iv administration of HN2. HN2 treatment produced nausea, vomiting, anorexia, alopecia, phlebitis, hepatotoxicity, and neurotoxicity. High-dose HN2 produced cardiotoxicity and hypocalcemia not found at lower doses. Nonhematological toxicity prevented use of higher doses. Granulocyte counts remained below 1.0 x 10(9)/liter for a mean of 10 days. Thrombocyte counts remained below 50.0 x 10(9)/liter for a mean of 8 days. HN2 treatment produced no response in MM. Although the study included no controls, transplantation of noncryogenically stored, syngeneic bone marrow apparently accelerates recovery of bone marrow function following chemotherapy when compared to patients not receiving such transplants. (27 Refs)

15. CHEMOIMMUNOTHERAPY FOR MELANOMA WITH DTIC, ACNU, VCR AND OK432: EVALUATION OF NEW COMBINATIONS FOR SURVIVAL RATES, SIDE EFFECTS AND CELLULAR IMMUNITY.

Jimbow K, Yanbe H, Nishio C
Dept. Dermatology, Sapporo Medical Coll., Minami 1, Nishi 16, Sapporo 060, Japan
J Dermatol (Tokyo); 8(4):259-266 1981

The effects of combined chemotherapy [5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, vincristine, and 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride] and immunotherapy (nonspecific Group A streptococcal preparation OK432) on eight disseminated melanoma patients were evaluated. The patients had primary lesions of histologically verified lentigo-maligna, Stage III or IV; 7/8 patients had lesions belonging to acral and mucosal malignant melanoma and 1/8 had primary occurrence on the back. Controls consisted of 11 Stage III melanoma patients with lentigo-maligna treated by other regimens of chemoimmunotherapy, immunotherapy, radiation, or a combination of these. Survival rates were significantly different at 5 and 8 mo after initiation of treatment from those exhibited by co ntrols; survival period ranged between 5 and 18 mo, including five patients who were still alive. Controls survived 3-15 mo, but all died. Blood picture and liver function tests before and after the trials revealed a decrease in RBC count and increase in serum glutamic oxalacetic transaminase, but the changes were within normal limits. Cellular immunity with specific mitogens of autologous and allogeneic melanoma cells and non-specific mitogens was preserved. Lymphocytes from melanoma patients possessed a high killer cell effect against melanoma cells; the effect was nonspecific as evidenced by the killing of control cells from acute myelocytic leukemia patients. Immunoadjuvant therapy with OK432 appears to affect the cellular immune response in a way similar to BCG. (26 Refs)

16. HORMONTHERAPY OF MALIGNANT MELANOMA: A REVIEW OF CLINICAL RESULTS (MEETING ABSTRACT).

Beretta G, Luporini G
Medical Oncology, San Carlo Borromeo Hospital, Milan, Italy
W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

Hormone - estrogen (ER), progesterone (PR), and androgen (AR) - receptors have been detected in biopsy samples of human melanoma. Initial data on im Medroxy-progesterone acetate (MPA) 300 mg/day or 600 mg/weekly reported objective response (OR equals reduction greater than 50% of tumor lesions) in 25% of 8 evaluable patients. Present available results with high doses (greater than 400 mg/day im or po) show 8.7% response rate in 23 evaluable patients. Diethylstilbestrol produced 8.3% OR in 24 evaluable patients. The OR were achieved in males and peculiarly both patients were ER - at biopsy. Pregnenetrione - which has an antiestrogen and glucocorticoid activity - did produce 7.1% OR in 155 evaluable patients. Tamoxifen citrate was able to induce 10.4% OR in 105 evaluable patients. No clinical paper has been published concerning specific antimelanoma activity of androgens and/or corticosteroids: after Dexamethasone, often given at high doses in the presence of brain metastases, no control of the other parametrable lesions was achieved. Even if the therapeutic effects of hormone therapy are generally low (less than 10% OR), a more extensive experience is needed, especially considering: a) the limited response rate after the first line agents (usually Dacarbazine and/or Nitrosoureas); b) the very poor activity of any second line therapy after initial treatment failure; c) the negligible toxicity and in some instance the subjective benefits produced by the hormonal treatment. (5 Refs)

OTHER THERAPEUTIC MODALITIES

17. EFFECT OF PUVA AND SUP THERAPY ON NEVUS-CELL NEVI.

Pullmann H, Theunissen A, Galosi A, Steigleder GK
Universitats-Hautklinik, Joseph-Stelzmann-Str. 9, D-5000 Koln 41, W. Germany
Z Hautkr; 56(21):1412-1417 1981

The effect of exposure to UV rays on nevus-cell nevi (NCN) was studied in 36 patients with psoriasis. Thirteen NCN were treated according to selective UV phototherapy (SUP; emission density 3.6 milliWatts/square cm), 23 others according to the PUVA therapy (psoralen plus type A rays; emission density 7 milliWatts/square cm). Increase in the av size of the NCN from 4.7 to 5.3 square mm was seen in 28.36 cases after 15 irradiations (4 wk). Significant darkening of 15/36 NCN was observed. There was no correlation between darkening and the increase in size, and there was no significant difference as a function of the therapy form. Autoradiography of excised nevi showed increased proliferation of melanocytes, keratinocytes, and dermal cells in exposed nevi compared with unexposed controls. (23 Refs) (In GER)

MULTIMODAL THERAPY

18. REDUCED INCIDENCE OF LOCO-REGIONAL RECURRENCES IN MELANOMA USING BCG IMMUNOTHERAPY AFTER SURGERY (MEETING ABSTRACT).

Paterson AH, Williams D, Jerry LM, McPherson TA
Cross Cancer Institute, Alberta T5G 1Z2, Canada
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

A prospectively controlled, randomized clincal trial was carried out to determine whether a combination of local perilesional id and systemic oral BCG immunotherapy given after surgery to patients with early melanoma would reduce the overall recurrence rate and improve survival. Patients with Stage I melanoma, Clark's Level (CL) 3-5 were eligible for trial entry, and after surgical wide excision and consent, were randomly allocated to either routine follow-up or adjuvant BCG immunotherapy. Immunotherapy consisted of id BCG 40 mg by Heaf Gun around the site of local surgery followed by oral BCG 40 mg for 5 days each mo for one yr. ID BCG was then repeated at the same site and oral BCG was continued for one further yr. One hundred and fifty-eight patients were entered into the trial: 79 in the treatment group (of whom 53 were CL 3, 23 were CL 4, and 3 were CL 5) and 79 in the control group (of whom 51 were CL 3, 25 were CL 4 and 3 were CL 5). There have been 36 recurrences: 14 in the treatment group and 22 in the control group. Twenty-one patients have died: 9 in the treatment group and 13 in the control group. Using this form of immunotherapy, there has been a significant reduction in the incidence of local and regional recurrences as site of first recurrence (5 BCG vs 17 control) but not of distant metastases (9 BCG vs 5 control). The overall recurrence rates show a trend in favor of the BCG group, which is entirely due to the reduction of loco-regional recurrences in this group. (no Refs)

CASE REPORTS

19. 'PURE' CUTANEOUS HISTIOCYTOSIS-X.

Wolfson SL, Botero F, Hurwitz S, Pearson HA
Edward Mallinckrodt Inst. Radiology, Div. Radiation Oncology, Washington Univ. Sch. Medicine, 510 South Kingshighway, St. Louis, MO, 63110
Cancer; 48(10):2236-2238 1981

The case histories of two young children who experienced skin rashes involving various areas of the body are reported. The diagnosis of pure cutaneous histiocytosis-X was established after extensive studies revealed no other organ involvement. The patients were treated with oral corticosteroids. Currently, both children are in good health, show no evidence of disease, and have been followed over a 4-to-5-yr period. Therapy with corticosteroids may not be indicated with pure cutaneous histiocytosis-X unless there is evidence of extracutaneous dissemination or rapid progression of the disease. (Author abstract) (12 Refs)

20. NECROSCOPIC FINDINGS OF PLEOMORPHIC, VARIABLY ACID-FAST BACTERIA IN A FATAL CASE OF KAPOSI'S SARCOMA.

Cantwell AR, Lawson JW
4900 Sunset Blvd., Los Angeles, CA, 90027
J Dermatol Surg Oncol; 7(11):923-930 1981

The presence of acid-fast and other bacteria was studied in a fatal case of Kaposi's sarcoma (KS). A 74-yr-old man died with cutaneous and visceral involvement of KS. The first biopsy-proven lesion of KS had appeared 2 yr previously as a small, red, rubbery tumor on the left upper retromolar area. Upon autopsy, sections of the myocardium showed multiple foci of acid-fast, variably sized coccoid and rod forms. The lungs contained many foci of highly pleomorphic bacteria; the microbes were Gram-positive and non-acid-fast. The esophagus showed multiple areas of ulceration, in which myriads of cocco-bacillary and filamentous, non-acid-fast and Gram-positive forms were evident. The small and large bowel also contained bacterial foci. Sections of cutaneous lesions of KS revealed rare foci of non-acid-fast, variably sized coccoid forms associated with the lesions in the dermis. Similarly stained granular structures, with variably sized coccoid elements at their periphery, were observed sparsely in the upper dermis, at the dermal-epidermal junction, and in the basal-cell layer of the epidermis. These forms were similar to forms observed in the intestinal wall. Similar granular forms were observed throughout the connective tissue. The role of bacteria in etiology of KS is discussed. (34 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

21. PERSPECTIVES IN THE EPIDEMIOLOGY OF MELANOMA (MEETING ABSTRACT).

van der Esch EP, Stukonis MK
Antoni van Leeuwenhoekziekenhuis, Amsterdam, The Netherlands
W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

UV irradiation appears to be a factor in the carcinogenesis of melanoma for the fair skinned population. Is an association with other factors existing? A very low correlation was found wit h sunlight related sites of cancer such as lips and skin. The correlation is strong for females with ovarian cancer. The aim of the study is to indicate methods for investigations exploring the apparently inconsistent findings. The melanoma incidence of three areas has been analyzed for the functions of age, sex and sites. Concluding that the genesis of melanoma is also determined by endogenous host factors, further research should include: a) Population-based registration of melanoma for cohort studies, studies on migrant populations and populations characterized by their way of life. b) Studies on correlation with other malignancies, with avoidable circumstantial factors and with endogenic factors. c) Case-control studies should complement the studies to define attributable risks. Exposed and non-exposed anatomical sites should be considered separately for incidental overdose and cumulative effects of prolonged exposure. (no Refs)

22. WHICH MOLES MATTER? THE ASSOCIATION BETWEEN MELANOCYTIC NAEVI AND MALIGNANT MELANOMATA.

MacKie RM
Dept. Dermatology, Univ. Glasgow, Anderson Coll. Building, 56 Dumbarton Road, Glasgow G11 6NU, Scotland
Br J Dermatol; 105(5):607-609 1981

The association of skin melanomas with adjacent or pre-existing nevi is reviewed; the true relationship between benign and malignant melanocytic lesions of the skin remains to be established. For the dermatologist the belief that melanocytic nevi on the palms, soles, and genitalia are more likely to undergo malignant change must be questioned. Follow-up examinations of melanoma patients after surgery should involve more than local inspection and palpation of the draining lymph node system. (10 Refs)

23. TUMOUR SPECTRUM IN THE FAMMM SYNDROME.

Lynch HT, Fusaro RM, Pester J, Oosterhuis JA, Went LN, Rumke P, Neering H, Lynch JF
Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE, 68105
Br J Cancer; 44(4):553-560 1981

The familial atypical multiple mole-melanoma syndrome (FAMMM) is characterized by an autosomal dominantly inherited susceptibility to multiple atypical nevi. patients with this hereditary phenotype show a strong susceptibility to cutaneous malignant melanoma (CMM). Our investigation of an extended Dutch kindred showing the FAMMM phenotype revealed a proband with bilateral intraocular malignant melanoma (IOM) and multiple CMM. The family revealed an array of tumors which included carcinoma of the lung, skin, larynx, and breast in addition to CMM and IOM, which were transmitted vertically through three generations. There was male-to-male transmission, and the number of affected males and females was about the same, which was consistent with an autosomal dominant inheritance. Thus the FAMMM syndrome not only indicates a potential for CMM, but a susceptibility to other systemic cancers as well. These observations, though limited to a single kindred, merit a painstaking evaluation of cancer of all anatomical sites in other kindreds showing the FAMMM syndrome. Such studies could yield clues to cancer etiology, pathogenesis, and control. (Author abstract) (22 Refs)

24. CIGARETTE SMOKING AND MALIGNANT MELANOMA. PROGNOSTIC IMPLICATIONS.

Rigel DS, Friedman RJ, Levine J, Kopf AW, Levenstein M
Skin and Cancer Unit, New York Univ. Medical Center, 566 First Ave., New York, NY, 10016
J Dermatol Surg Oncol; 7(11):889-891 1981

The influence of cigarette smoking on metastatic potential of malignant melanomas was examined. Histories of cigarette smoking were obtained from 178 patients with primary cutaneous malignant melanoma. Because almost 80% of recurrences in the study occurred in the first 24 mo following locally definitive surgery, a 2-yr metastasis-free rate was used in calculations. Of the 178 patients, 48 were currently cigarette smokers, 68 former smokers, and 62 had never smoked. During the period of the study 19 patients developed metastases. Only 33 patients were included in the high-risk group (current smokers with histories of greater than 15 pack-yr; 1 pack-yr = 1 pack/day for 1 yr); 8/19 of the recurrences occurred in this subset. In contrast, the low-risk group (145: non-smokers, former smokers, and current smokers with histories of less than or equal to 15 pack-yr) accounted for only 11/19 of the metastases. The difference in 'expected vs observed metastases' in the two groups was statistically significant ($p = 0.008$). Mean thickness of the lesions for high- and low-risk patients was 2.04 +-1.87 mm and 1.60 +-1.40 mm, respectively. No significant difference was found between high- and low-risk groups with regard to age or sex. The results indicated an increased risk of metastasis in patients with malignant melanomas who are currently smokers with greater than 15 pack-yr histories compared to those with less than or equal to 15 pack-yr. (8 Refs)

25. HABITS OF SUN EXPOSURE AND RISK OF MALIGNANT MELANOMA: AN ANALYSIS OF INCIDENCE RATES IN NORWAY 1955-1977 BY COHORT, SEX, AGE, AND PRIMARY TUMOR SITE.

Magnus K
Cancer Registry Norway, Montebello, Oslo 3, Norway
Cancer; 48(10):2329-2335 1981

Incidence data on malignant melanoma of the skin in Norway from 1955-1977, comprising a total of 5,108 new cases, were analyzed according to cohort, sex, age, and primary tumor site. A continuous increase in incidence of approx 7% per yr was observed for both sexes during the study period. For trunk and lower limb melanomas, the increase and cohort variations in incidence were much greater than for face and neck melanoma. A difference between these site groups was also observed in the shape of the cohort curves of age-specific rates. This indicated that the trend in carcinogenic exposure through life was different for the face-neck and the trunk-lower limb. For the generations born 1930-1949, the incidence of malignant melanoma per area unit of skin was greater for the trunk and lower limb than for the face-neck. It is suggested that not only the cumulated dose, but also the intensity of solar radiation may be significant in the cause of malignant melanoma. (Author abstract) (9 Refs)

26. PNEUMOCYSTIS CARINII PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN. EVIDENCE OF A NEW ACQUIRED CELLULAR IMMUNODEFICIENCY.

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A
Dept. Medicine, UCLA Sch. Medicine, Center for the Health Sciences, Los Angeles, CA, 90024
N Engl J Med; 305(24):1425-1431 1981

An acquired T-cell immunodeficiency is reported in four previously healthy homosexual men. All patients experienced malaise, fever, and lymphadenopathy for several mo prior to onset of more specific symptoms. All contracted Pneumocystis carinii pneumonia, extensive mucosal candidiasis, and multiple viral infections. Cytomegalovirus was found in the secretions of all patients, and Kaposi's sarcoma developed in one patient 8 mo after he presented with esophageal candidiasis. Antibodies to Epstein-Barr virus and hepatitis B were detected in the other three. Monoclonal-antibody analysis of peripheral blood T-cell subpopulations revealed an inversion of the T helper to suppressor/cytotoxic ratio. The association between chronic cytomegalovirus infection and Kaposi's sarcoma is discussed, and a relationship between the immunodeficiency syndrome and the recent appearance of Kaposi's sarcoma in the male homosexual population is suggested. Cytomegalovirus infection could be a result rather than a cause of the T-cell defect; exposure to an undetected microorganism, drug, or toxin may have made these patients susceptible to infection by opportunistic organisms including cytomegalovirus. (41 Refs)

27. AN OUTBREAK OF COMMUNITY-ACQUIRED PNEUMOCYSTIS CARINII PNEUMONIA. INITIAL MANIFESTATION OF CELLULAR IMMUNE DYSFUNCTION.

Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, Wormser G, Brettman L, Lange M, Murray HW, Cunningham-Rundles S
Cornell Medical Coll., A-431, 1300 York Ave., New York, NY, 10021
N Engl J Med; 305(24):1431-1438 1981

Eleven cases of cellular immunodeficiency associated with Pneumocystis carinii pneumonia are reviewed. Patients were all men (27-40 yr old) who were either drug abusers (7) or homosexuals (6) or both (2). One patient had a cutaneous lesion revealed by biopsy to be Kaposi's sarcoma (KS). One other had angioimmunoblastic lymphadenopathy (AL). Eight patients died. The observed immune dysfunction could have been associated with KS and AL. (35 Refs)

28. OPPORTUNISTIC INFECTIONS AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Durack DT
Duke Univ. Medical Center, Durham, NC, 27710
N Engl J Med; 305(24):1465-1467 1981

Current data and theories concerning opportunistic infections and Kaposi's sarcoma in homosexual men are reviewed. Patients are typically young and live in large cities, and many use drugs. Infectious agents are low grade pathogens that often cause opportunistic infections in compromised hosts, and the death rate is very high. The immunodeficiency is cellular rather than humoral, and the gap in host defenses is not limited to those against any one class of microbe. Evidence of previous or current cytomegalovirus infection is a common finding. Kaposi's sarcoma is found in young Africans, elderly Americans, renal-transplant recipients, and homosexual men. The discovery of cytomegalovirus genome in Kaposi's sarcoma tissue indicates the possibility of a cause-effect relationship between the virus and the tumor; some new factor may have distorted the host-parasite relation. Recreational drugs such as amyl nitrite may combine with the effects of persistent viral infection to cause immunosuppression in some genetically predisposed men. (16 Refs)

SELECTED PRECLINICAL STUDIES

29. COMPARISON OF TWO SOFT-AGAR METHODS FOR ASSAYING CHEMOSENSITIVITY OF HUMAN TUMOURS IN VITRO: MALIGNANT MELANOMAS.

Tveit KM, Endresen L, Rugstad HE, Fodstad O, Pihl A
Norsk Hydro's Inst. Cancer Res., Montebello, Oslo 3, Norway
Br J Cancer; 44(4):539-544 1981

Two soft-agar methods for assaying chemosensitivity of human cancers in vitro were compared with respect to colony morphology, plating efficiency (PE) and chemosensitivity of human melanomas. In nine xenografts and nine patients' biopsy specimens Method A (essentially that of Courtenay and Mills, 1978) gave considerably higher PE than Method B (essentially that of Hamburger and Salmon, 1977) and, in contrast to Method B, the number of colonies was proportional to the number of cells plated. Evidence was obtained that the observed differences in PE could be attributed to the low O2 concentration and the presence of rat RBC in Method A. Colony morphology was similar in the two assays. When cells from four xenografted melanomas were treated in vitro with dacarbazine, semustine, vinblastine and abrin, and the inhibition of colony formation was assayed concurrently in the two soft-agar methods, the tumor cells appeared to be more sensitive to three of the drugs in Method B than in A. The results demonstrate that chemosensitivity data obtained with the two assays cannot be directly compared. (Author abstract) (16 Refs)

30. THE ROLE OF FIBRONECTIN IN ADHESION OF METASTATIC MELANOMA CELLS TO ENDOTHELIAL CELLS AND THEIR BASAL LAMINA.

Nicolson GL, Irimura T, Gonzalez R, Ruoslahti E

Dept. Tumor Biology, Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030

Exp Cell Res; 135(2):461-465 1981

Vascular endothelial cells synthesize an extracellular matrix or basal lamina composed of collagens, proteoglycans and glycoproteins such as fibronectin (FN). Using affinity-purified anti-FN, we have examined the role of FN in adherence of metastatic B16 melanoma cells to endothelial cell monolayers which lack FN on apical cell surfaces and to their basal lamina which contains FN. B16 melanoma cells, which do not contain significant amounts of FN, attached at much higher rates to endothelial basal lamina and polyvinyl-immobilized FN compared with intact endothelial cell monolayers. Anti-FN failed to inhibit attachment of melanoma sublines of low (B16-F1) or high (B16-F10) metastatic potential to intact endothelial cell monolayers, inhibited slightly B16 cell attachment to basal lamina and completely abolished attachment of B16 cells to polyvinyl-immobilized FN. The antibiotic tunicamycin which inhibits glycosylation of B16 cell surface glycoproteins and blocks experimental metastasis inhibited B16 attachment to endothelial cells, basal lamina and immobilized FN. The results suggest that FN mediates, only in part, the adhesion of B16 melanoma cells to basal lamina through glycoprotein receptors on B16 cells. (Author abstract) (38 Refs)

31. INHIBITION OF EPIDERMAL GROWTH FACTOR BINDING BY PROSTAGLANDIN A'S.

Lee LS

Dept. Res. Development, General Electric, Schenectady, NY

Biochem Biophys Res Commun; 102(4):1144-1150 1981

The effects of various prostaglandins on the binding of 125I-labeled epidermal growth factor (EGF) to a number of cell lines were investigated. Prostaglandin A1 and prostaglandin A2 (16 ug/ml) exerted rapid, dose-related inhibition of 125I-EGF binding to cell lines MRC-5, HeLa, XP, WI38, and 10T1/2, whereas prostaglandins E1, E2, F1-alpha, B2 and F2-alpha-tromathamine in the concentration range 0.026-54 ug/ml had little or no effect. The 50% binding-inhibition doses for PGA1 and PGA2 in HeLa cells were 7 ug/ml for 17 ug/ml, respectively, when tested with 125I-EGF at 0.5 nanog/10(6) cells. PGA1 and PGA2 did not inhibit the binding of labeled insulin, multiplication-stimulating activity, human growth hormone, concanavalin A, or phorbol 12,13-dibutyrate. These results show that the A-series prostaglandins can be used as a probe to investigate the EGF-receptor system. Since compounds that inhibit EGF binding are often tumor promoters, the results also suggest that substances such as PGA's, when present at high concentrations, may be tumor promoting. (25 Refs)

32. EVIDENCE THAT VIRAL TRANSFORMING GENE PRODUCTS AND EPIDERMAL GROWTH FACTOR STIMULATE PHOSPHORYLATION OF THE SAME CELLULAR PROTEIN WITH SIMILAR SPECIFICITY.

Erikson E, Shealy DJ, Erikson RL
Dept. Pathology, Univ. Colorado Sch. Medicine, Denver, CO, 80262
J Biol Chem; 256(22):11381-11384 1981

Treatment of A-431 human epidermoid carcinoma cells with epidermal growth factor (EGF) was shown to enhance the phosphorylation of a Mr = 34,000 protein. Because the phosphorylation of an analogous protein is enhanced in various cell lines transformed by Rous sarcoma virus (RSV) we characterized the phosphorylation of the A-431 Mr = 34,000 protein under these two conditions in order to determine whether there are common pathways between viral transformation and EGF stimulation. The results of tryptic phosphopeptide mapping and phosphoamino acid analysis showed that the Mr = 34,000 protein was phosphorylated in an identical manner by the EGF-stimulated protein kinase activity and by the protein kinase activity of the RSV transformation-specific protein or of its normal cell homolog. Although the specific protein kinase that phosphorylates the Mr = 34,000 protein under conditions of EGF-stimulation is not yet identified, these studies demonstrate that at least one consequence of EGF stimulation is identical with one of the consequences of viral transformation. (Author abstract) (43 Refs)

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Diagnosis, Treatment

SERIES CT22 No. 82/05

MAY, 1982

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DIAGNOSIS

1. SCINTIGRAPHIC IDENTIFICATION OF LYMPHATIC DRAINAGE OF MALIGNANT MELANOMA OF THE TRUNK.

Altmeyer P, Munz D, Steinhoff W, Hor G, Holzmann H
Zentrum der Dermatologie und Virologie, Theodor Stern Kai, D-6000 Frankfurt/M., W. Germany
Aktuel Dermatol; 7(5):127-130 1981

Lymphoscintigraphy (LS) was performed on 21 patients with malignant melanoma (MM) of the trunk. MM types included superficially spreading (11 cases), primary nodular (6 cases), lentigo maligna (2 cases), and unclassifiable (2 cases). LS was performed preoperatively and ipsilaterally in 13 cases, postoperatively and ipsilaterally in 5 cases, and postoperatively and contralaterally in 3 cases. Contralateral LS was done to determine the original lymphatic drainage of the excised tumor, on the assumption of symmetrical lymphatic patterns. LS followed injection of 1.5-2.0 mCi 99mTc-labeled colloidal antimony sulfide divided among 4-6 sites 0.5-1 cm from the edge of the tumor (or along the edge of scar tissue in postoperative LS), injected intracutaneously and sc. As indicated by

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five case examples, lymphatic drainage varied greatly from one individual to another, preventing any general anatomical conclusions. Tumors in the region of Sappey's veins showed particularly variable drainage to axillary and/or inguinal lymph nodes. Results demonstrate the utility and low risk of LS for individual determination of lymphatic regions at risk due to MM. (10 Refs) (In GER)

2. GENETIC AND CELLKINETIC CHARACTERIZATION OF MALIGNANT MELANOMAS BY FLOW CYTOMETRY (MEETING ABSTRACT).

Schumann J, Gonde W, Bruchmuller S, Straub C

University of Munster, 4400 Munster, W. Germany

VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

In 250 patients with malignant melanomas the DNA-distribution patterns of 95 primary tumors and of 316 metastasis were determined by flow cytometry using an ICP. Aneuploid cell lines could be identified in 82% of all patients, 72% of the aneuploid lines were in the tritetraploid range. Thirty-eight percent of the primary tumors showed more than one malignant cell line, they were multiclonal, whereas this rate in metastasis was below 10%. Ploidy was quanitified by DNA-Index (DNA-Index equals 2 stands for normal G1-cells with diploid DNA-content). The mean DNA-Index of all melanomas was 3.3. In melanomas with Clark's level II the mean DNA-Index was 3.5, with level III 3.3, with level IV 3.1 and with level V 2.9. The rate of aneuploidies was higher in level V (86%) than in level IV and III (each 80%) or level II (68%). Male patients had 88% aneuploidies with a mean-DNA-Index of 3.1, females 76% aneuploidies with a mean-DNA-Index of 3.4. The S-phase-fraction (mean 14.4%) was not correlated with certain ploidy stages but was a little bit higher in the triploid range than in the tetraploid range or the near diploid range. Tumors with higher S-phase fractions seem to be more sensitive to chemotherapy. In a number of patients different metastasis with genetical different cell lines could be detected at the same time. (no Refs)

3. RELATIONSHIP BETWEEN PATIENTS' EARLY RECOGNITION OF MELANOMA AND DEPTH OF INVASION.

Cassileth BR, Clark WH, Heiberger RM, March V, Tenaglia A

Psychosocial Program, Univ. Pennsylvania Cancer Center, Hosp. Univ. Pennsylvania, 7 Silverstein Pavilion, 3400 Spruce St., Philadelphia, PA, 19104

Cancer; 49(1):198-200 1982

The correlation between time to diagnosis and thickness of lesion in patients with superficial spreading melanoma was explored. Charts of 245 patients diagnosed since 1976 were reviewed for data on lesion duration and time since elevation (as perceived by patients); and the degree of elevation (if any), thickness, and diameter of lesion (as measured histologically). No correlation emerged between time to diagnosis and the biologic state of disease as reflected by thickness. The majority of melanomas in this series were not recognized by patients in an early, pre-elevation, low-risk phase. Whether an emphasis on identification of melanoma in this phase will lead to an increase in the percent of patients presenting with biologically early, curable disease remains to be tested. (Author abstract) (6 Refs)

4. UVEAL MELANOMA IN CHILDREN AND ADOLESCENTS.

Barr CC, McLean IW, Zimmerman LE
(c/o McLean) Dept. Ophthalmic Pathology, Armed Forces Inst. Pathology, Washington, DC, 20306
Arch Ophthalmol; 99(12):2133-2136 1981

Five-year survival data were available in 78 cases originally classified as uveal melanomas in patients less than 20 years old. Forty-two were malignant melanomas arising from the choroid and/or ciliary body; 13 patients from this group died of metastatic disease. Factors that significantly correlated with fatality were a red, painful eye, extraocular extension at enucleation, basal tumor diameter greater than 10 mm, increased mitotic activity, and tumor necrosis. There were 36 iridic tumors; nine were reclassified as nevi. Of the 27 patients with iridic melanomas, only four died of metastases. The predominant factors relating to fatal outcome were glaucoma, extension of tumor into the ciliary body, diffuse growth, deep angle invasion, scleral invasion by tumor cells, and increased mitotic activity. Except for their relative rarity, uveal melanomas in children and adolescents did not differ significantly from their counterparts in adults. (Author abstract) (28 Refs)

5. ARE MOST IRIS 'MELANOMAS' REALLY NEVI? A CLINICOPATHOLOGIC STUDY OF 189 LESIONS.

Jakobiec FA, Silbert G
Manhattan Eye, Ear, and Throat Hosp., 210 E 64th St., New York, NY, 10021
Arch Ophthalmol; 99(12):2117-2132 1981

A retrospective clinicopathologic study of 189 iris and iris and ciliary body lesions originally diagnosed as melanomas led to a nine-part histopathologic classification. Eighty-seven percent of lesions were reassigned to six benign categories and 13% were assigned to three malignant ones (spindle-B and epithelioid cell melanomas). There were no tumor deaths. The benign lesions were so classified if the constituent cells displayed bland cytologic characteristics, even though they might have produced a surface plaque or growth onto the trabecular meshwork and peripheral cornea. No clinical features were found to distinguish the benign from malignant tumors, including diffuse spread and the presence of glaucoma. The six recurrent tumors were equally divided between benign and malignant lesions. Thirty-six of 42 patients with incompletely excised lesions did not show further clinical problems on followup, establishing the inherently benign nature of most of the tumors. (Author abstract) (39 Refs)

6. AMYLOID IN LOCALIZED CUTANEOUS AMYLOIDOSIS: IMMUNOFLUORESCENCE STUDIES WITH ANTI-KERATIN ANTISERUM ESPECIALLY CONCERNING THE DIFFERENCE BETWEEN SYSTEMIC AND LOCALIZED CUTANEOUS AMYLOIDOSIS.

Masu SI, Hosokawa M, Seiji M
Dept. Dermatology, Tohoku Univ., Sch. Medicine, 1-1 Seriyomachi, Sendai 980, Japan
Acta Derm Venereol (Stockh); 61(5):381-384 1981

Amyloids deposited in the skin in cases of systemic amyloidosis (SA) and primary and secondary localized cutaneous amyloidosis (LCA) were studied. Amyloid masses were larger in dermis from patients with SA than with LCA. In both cases, masses had a characteristic filamentous structure. Most amyloid masses stained for anti-keratin antibody; staining occurred in primary LCA (macular or lichen) and in LCA secondary to Bowen disease, basal cell carcinoma, or giant porokeratosis, but not in primary SA or SA associated with multiple myeloma. (9 Refs)

7. IMMUNO-ELECTRON MICROSCOPY OF 'T' CELLS IN LARGE PLAQUE PARAPSORIASIS.

McMillan EM, Wasik R, Martin D, Donaldson M, Everett MA

Dept. Dermatology, Univ. Oklahoma, Health Sciences Center, 619 N.E. 13th, Oklahoma City, OK, 73104

J Cutan Pathol; 8(5):385-392 1981

The peroxidase-antiperoxidase technique was used to demonstrate a specific surface human T lymphocyte antigen (HTLA) in atrophic large plaque parapsoriasis. Tissue specimens obtained from a 55-yr-old man with a 6-yr history of parapsoriasis were prefixed in paraformaldehyde before freezing, treated with anti-HTLA, and examined by transmission electron microscopy. Positive membranous staining indicating the presence of HTLA was observed in 70% of cells. A high proportion of cells had convoluted nuclei; approx 80% of cells with convoluted nuclei were HTLA positive. The findings suggest a relationship between the atrophic large plaque parapsoriasis and mycosis fungoides. (27 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

8. GRANULOMAS IN MELANOMA PATIENTS TREATED WITH BCG IMMUNOTHERAPY.

Hatzitheofilou C, Obenchain DF, Porter DD, Morton DL

(c/o Morton) 54-140 Center Health Sciences, Univ. California, Los Angeles, CA, 90024

Cancer; 49(1):55-60 1982

Autopsy slides from 22 melanoma patients who received bacille Calmette-Guerin BCG immunotherapy and who had a postmortem examination at the UCLA Center for the Health Sciences were examined for the presence of granulomas. Granulomas were found in six patients (29%) who received BCG but not in a group of 25 melanoma patients who did not have BCG immunotherapy. A number of factors were tested for correlation with the presence of granulomas in the autopsy material. Fifty-five percent of the patien ts who received BCG by both intralesional and tine technique developed granulomas. No patients given BCG by the tine technique alone developed granulomas. No correlation was found between granulomas and the presence of symptoms after the administration of BCG, the duration of BCG immunotherapy, the patient's age, the number of BCG administrations, treatment with immunosuppressive agents, the length of survival after the last BCG administration, the presence of a positive PPD reaction, a positive history for granuloma-forming diseases and tests for immunocompetence. However, these results provide evidence that the route of BCG administration strongly influences the frequency of granulomas in melanoma patients who received BCG immunotherapy. (Author abstract) (25 Refs)

CHEMOTHERAPY

9. ADJUVANT IMMUNOTHERAPY OR CHEMOTHERAPY FOR MALIGNANT MELANOMA.

Fisher RI, Terry WD, Hodes RJ, Rosenberg SA, Makuch R, Gordon HG, Fisher SG

Building 10, Room 12N226, NCI, Bethesda, MD, 20205

Surg Clin North Am; 61(6):1267-1277 1981

A prospective randomized clinical trial examined whether adjuvant immunotherapy or chemotherapy prolongs the disease-free interval and ultimate survival of patients with Stage I malignant melanoma or Stage II melanoma. Following surgical treatment, 166 patients were randomized to receive either no further treatment, BCG, BCG plus neuraminidase-treated allogeneic cells, or methyl-CCNU. No significant differences in time to recurrence were observed among the four groups, although the methyl-CCNU and BCG plus vaccine curves appeared to separate from the BCG and control arms at approx 1 yr. Improvement observed in methyl-CCNU patients appeared to result from improved prognosis of Stage I patients. The methyl-CCNU patients had slightly improved disease-free survival rates compared to controls, but the small number of patients in this subgroup makes a definitive statement difficult. Toxicity related to treatment is discussed. (12 Refs)

10. NEPHROTOXICITY OF SEMUSTINE (METHYL-CCNU) IN PATIENTS WITH MALIGNANT MELANOMA RECEIVING ADJUVANT CHEMOTHERAPY.

Micetich KC, Jensen-Akula M, Mandard JC, Fisher RI

(c/o Fisher), NCI, Building 10, Room 12N226, Bethesda, MD, 20205

Am J Med; 71(6):967-972 1981

The nephrotoxicity of semustine (methyl-CCNU) has been studied in 45 adult patients with surgically resected Stage I or II malignant melanoma who received this drug as adjuvant chemotherapy. Abnormalities of renal function (including three cases of renal failure) were noted in 7 of 45 patients (16%); all these patients received more than 1,400 mg/m2. This represents an incidence of 26% in patients receiving more than 1,400 mg/m2 semustine. Two distinct patterns emerged. Abnormal serum creatine levels developed in two patients while receiving semustine and later progressed to renal failure. Five patients h ad normal serum creatinine levels throughout their treatment courses but had abnormal creatinine values 1 mo to 2 yr following the completion of drug therapy. Renal failure developed in one of these patients, but the remaining four have had stable renal function for 1 to 2 yr of additional follow-up. No clinical signs of renal insufficiency were detected in any patients receiving less than 1,400 mg/m2 of semustine. No changes unequivocally attributable to semustine were seen in eight patients at autopsy despite the fact that three had received greater than 1,900 mg/m2 of nitrosourea. This incidence of nephrotoxicity appears to be significantly lower than that previously reported in children. Guidelines for future therapy with semustine are described. (Author abstract) (8 Refs)

11. CISPLATIN HYDRATION WITH AND WITHOUT MANNITOL DIURESIS IN REFRACTORY DISSEMINATED MALIGNANT MELANOMA: A SOUTHWEST ONCOLOGY GROUP STUDY.

Al-Sarraf M, Fletcher W, Oishi N, Pugh R, Hewlett JS, Balducci L, McCracken J, Padilla F

(c/o Southwest Oncology Group), Operations Office, 3500 Rainbow Blvd., Suite 100, Kansas City, KS, 66103

Cancer Treat Rep; 66(1):31-35 1982

In a prospective Phase II randomized trial, a dose of 100 mg/m2 iv cisplatin every 3 weeks plus forced hydration with or without mannitol diuresis was tested in patients with previously treated advanced malignant melanoma. A total of 67 patients were evaluated: 33 not given mannitol and 34 in the mannitol arm. Two partial remissions (of 2+ and 6.5 months) were achieved in the no-mannitol arm and one complete response and four partial responses (of 1, 2, 2.5, 5.5, and 8 months) were seen in the mannitol arm. Moderate, severe, and life-threatening renal toxicity was less in the mannitol arm, and patients tolerated more doses of cisplatin. The renal toxicity occurred mostly after the first dose of chemotherapy and did not seem to be cumulative. Other side effects were comparable in both arms. We concluded that renal toxicity is less severe in patients treated with cisplatin, hydration, and mannitol and that the use of cisplatin alone or in combination with other active agent(s) should be considered for further evaluation in previously untreated patients with malignant melanoma. (Author abstract) (18 Refs)

12. CHEMO-IMMUNOTHERAPY, IMIDAZOLE CARBOXAMIDE (DTIC) AND/OR LEVAMISOLE, IN TREATMENT OF MALIGNANT MELANOMA: PRELIMINARY RESULTS.

Perez Carrion R, Crespo Massieu C

Servicio de Radioterapia (Unidad de Oncologia), Centro Especial Ramon y Cajal, Madrid, Spain

Oncologia; 6(5):13-14,16-18,20-21 1981

Preliminary results obtained in treatment of 23 patients (13 men, 10 10 women; 20-73 yr old) with localized malignant melanoma (LMM) at high risk, and 11 patients with advanced malignant melanoma (AMM) were evaluated. Location of LMM was as follows: extremities (13), trunk and head (each 5). All patients with LMM were treated by resection and prophylactic lymphadenectomy. LMM patients were in Clark Stage III (3/23), Stage IV (14/23), and Stage V 5/23; in 21 cases lymph nodes were examined and 13 were positive. Seven patients received dimethyltriazenoimidazole carboxamide (DTIC) with levamisole (LEV), and 16 patients received only LEV. Dose of DTIC was 150 mg/square meter/day iv x5 every 6 wk; that of LEV 150 mg/day x3, with an interval of 14 days for a total of 12 mo. Follow-up examinations were made every 2 mo for a total of 3-30 mo. Of 23 patients 17 were in complete remission, of 7 relapses 5 were treated with LEV and 2 with LEV and DTIC. The difference in results between the two treatments was not significant. The AMM patients received DTIC with chloroethylcyclohexylnitrosourea (CCNU). Follow-up was from 3-30 mo. Of 11 patients, 9 could be evaluated and 3 were in partial remission. (33 Refs) (In SPA)

13. CLINICAL TRIALS OF CHEMOTHERAPY AND CHEMOIMMUNOTHERAPY IN PRIMARY MALIGNANT MELANOMA.

Jacquillat C, Banzet P, Maral J

Unite de Chimiotherapie, Institut de Recherches sur les Melanomes Malins, Lariboisiere Saint-Louis, 2 Place du Docteur Fournier, F-75475 Paris Cedex 10, France

Recent Results Cancer Res; 80:254-258 1982

We report here two randomized prospective clinical trials of adjuvant treatment in the management of primary malignant melanoma of Clark's Level III, IV or V. All patients had curative resection of the primary tumor. In the first trial, 117 patients were randomized between control (surgery alone) systemic chemotherapy and intraarterial chemotherapy. Intraarterial chemotherapy consisted of DTIC 80 mg/m2 + 8 days prior to surgery. Systemic chemotherapy consisted of courses of vinblastine (6 mg/m2), thiotepa (6 mg/m2), rufocromycine (60 ug/m2), methotrexate (15 mg/m2) on day 1, and procarbazine (30 mg/m12) x 7 days. Courses were repeated every 2 wk x 6, then every 4 wk x 15. Twenty-two of 55 patients relapsed in the control group vs 22 of 67 in the chemotherapy group (NS). For male patients, the difference in disease-free survival was significant (p less than 0.005, log rank test), though not in women. In the second trial, 352 patients were entered from July, 1976. Men were randomized between chemotherapy and chemoimmunotherapy. Women were randomized between surgery alone and chemoimmunotherapy. Chemotherapy was identical, except for the addition of DTIC (300 mg/m2) for each course. Immunotherapy consisted of BCG every 4 wk and C parvum every wk. Immunotherapy seemed to be of no additional benefit. (Author abstract) (5 Refs)

RADIOTHERAPY

14. RADIOTHERAPY IN NONLENTIGINOUS MELANOMA OF THE HEAD AND NECK.

Harwood AR, Dancuart F, Fitzpatrick PJ, Brown T

Dept. Radiation Oncology, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada

Cancer; 48(12):2599-2605 1981

Thirty-seven patients with superficial spreading or nodular melanoma of the head and neck treated with irradiation are reviewed. Twenty-one patients were referred within 3 mo of surgery. Six had an incisional biopsy followed by postoperative irradiation, four were locally controlled (1 dying of metastatic melanoma, 2 dying of intercurrent disease and 1 is alive and well), and two were not (both dead of melanoma). Fifteen patients had a local excisional biopsy (11 having tumor to the limits of the excision) followed by postoperative irradiation. Fourteen of the 15 had local control (3 had lymph node metastases and died, 3 died of distant metastases from melanoma, 7 are alive and well from 1-14 yr following treatment, and one is dead of intercurrent disease), and 1 had a local recurrence and subsequently died of metastatic melanoma. Sixteen patients were irradiated for iocal and/or regionally recurrent disease following unsuccessful surgery, and only two were successfully controlled by irradiation and are alive and well at 4 and 5 yr, respectively. Local control was 70% when a dose per fraction of greater than 400 rads was used, compared with 25% when a dose per fraction of less than 400 rads was used. It is concluded that nonlentiginous melanoma of the head and neck is not a radioresistant tumor and that local excision followed by high dose per fraction radiotherapy deserves further study in the management of melanomas of the head and neck. (Author abstract) (13 Refs)

15. KAPOSI'S SARCOMA. AN UPDATE ON THE RESULTS OF EXTENDED FIELD RADIOTHERAPY.

Harwood AR
Princess Margaret Hosp., 500 Sherbourne St., Toronto M4X 1K9, Ontario, Canada
Arch Dermatol; 117(12):775-778 1981

This report reviews the results of extended field radiotherapy (EFR) in the treatment of Kaposi's sarcoma. During the 22-yr period that is under study, 54 patients with Kaposi's sarcoma were seen and 38 were treated with EFR. Thirty patients had spontaneous Kaposi's sarcoma and eight had received immunosuppressive therapy. Extended field radiotherapy is compared with both local methods of radiation and chemotherapy in the treatment of Kaposi's sarcoma. It was concluded that EFR is the treatment of choice because of its simplicity, high disease-control rate, and lack of complications in patients without systemic disease manifestations. (Author abstract) (5 Refs)

16. TREATMENT OF BASAL CELL EPITHELIOMA WITH HIGH ENERGY ELECTRON BEAM.

Ogawa Y, Kumano M, Kumano K, Shimizu R, Imanaka K, Takashima H, Tsuboi Y, Okuno T, Yoshida M, Miyaji C, Imajo Y, Kimura S
Dept. Radiology, Hyogo Cancer Hosp., Hyogo, Japan
Gan No Rinsho; 27(14):1697-1700 1981

Treatment with high-energy electron beam radiotherapy of 30 patients (14 men, 16 women; 20-91 yr old) who had basal cell epithelioma was reported. Tumors were located on the head in 6 cases, face in 23, and back of the hand in 1. According to tumor, node, metastasis criteria, 16 tumors were T1N0M0, 11 were T2N0M0, and 3 were T3N0M0. Therapy consisted of 6 Mega electron volt beam radiotherapy delivered in 200 rad doses, 5x/wk, for a total of 4,800-12,000 rads with either a BMR-18 type betatron or a linac-12 type linear accelerator. The radiation field extended 0.5-1 cm around the tumor border. All of the tumors disappeared after radiotherapy, and all but one of the patients were without evidence of recurrence 2-12 yr after therapy. Recurrence was observed yr 2 in one patient, but the patient was without evidence of recurrence 5 yr 11 mo after surgical excision of the recurrent tumor. Four patients died during the observation period, but the deaths were not directly due to the tumors. (8 Refs) (In JPN)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

17. ULTRAVIOLET LIGHT SENSITIVITY AND PROLONGED UVR-ERYTHEMA.

Wilson PD, Kaidbey KH, Kligman AM
(c/o Kaidbey), 3401 Market St., Suite 226, Philadelphia, PA, 19104
J Invest Dermatol; 77(6):434-436 1981

We have compared the erythema and tanning responses in skin Type I (n = 15) and skin Type IV (N = 17) Caucasoids following a single exposure to solar simulated radiation. The former sunburn easily and do not tan while the latter do not burn and tan readily. The dose of radiation was 5x the Minimal Erythema Dose (MED). The test sites were the extensor aspect of the forearm (exposed site) and flexor aspect of the upper arm (nonexposed site). The responses were monitored at 24 and 48 hr and then twice weekly for 8 weeks. The group of skin Type I individuals had a lower MED and a much more prolonged erythema on both the exposed and nonexposed sites than the group of Type IV individuals. All differences were highly significant (p less than 0.005). After 4 weeks erythema remained present in all of the Type I subjects but had disappeared in 16 of the 17 Type IV subjects. Within the groups there was no difference between erythema duration on exposed vs nonexposed sites, but there was a highly significant difference (p less than 0.005) between the lower MED on the upper arm and higher MED on the forearm. These results contrast with those of other reports in which prolonged erythema could not be correlated with fair complexion, sunburn sensitivity, ethnic background, or skin type but was instead found to be a distinct feature of persons who had developed nonmelanoma skin cancer. Since prolonged erythema is related to skin type it is therefore not solely a feature of patients with skin cancer. (Author abstract) (10 Refs)

18. THE INFLUENCE OF CORNEAL STRATUM HYDRATION ON THE CHRONOLOGICAL DEVELOPMENT OF ACUTE ULTRAVIOLET INJURY.

Blazek V, Wienert V
Institut fur Hochfrequenztechnik RWTH Aachen, Melatener Str. 25, D-5100 Aachen, W. Germany
Strahlentherapie; 157(4):280-286 1981

The influence of corneal hydration on the reflectiveness of skin and on UV-induced damage was determined by an optical-electronic spectral method. Theoretical aspects are discussed. The biological effect of UV is dependent on the dose reaching living skin and arises from radiation absorption facilitated by photochemical effects. Knowledge of the absorptiveness of the corneal layers is important in UV therapy. Calculation of the absorption/scattering ratio in the UV range of the electromagnetic spectrum ('the Kubelka-Munk-function') is presented. Scattering of incident rays by inhomogeneities and phase-boundaries of the tissues has a decisive effect on overall reflection, which assumes a diffuse type. Because of the individual character of the reflection index of human skin, which is dependent on several factors, photometric study of reflection is possible only by means of the so-called 'Kugel mass geometric (2-way) test'. (18 Refs) (In GER)

SELECTED PRECLINICAL STUDIES

19. A BIOCHEMICAL AND BIOSYNTHETIC ANALYSIS OF HUMAN-MELANOMA-ASSOCIATED ANTIGENS WITH MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Bumol TF, Harper JR, Chee DO, Reisfeld RA
Scripps Clinic and Research Foundation, La Jolla, CA, 92037
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Two monoclonal antibodies (MoAbs 9.2.27 and F11) directed to cell surface and secreted melanoma associated antigens, respectively, were used to study the expression, biosynthesis and molecular nature of these glycoconjugated molecules. MoAb 9.2.27 detected from 1-2 x 10(5) antigenic sites per cell in direct binding studies of several melanoma cell lines. Analysis of subcellular fractions of these cells by the same method indicated that nearly all antigenic activity was in crude membrane fractions. Sodium dodecyl sulfate -polyacrylamide gel electrophoresis (SDS-PAGE) analyses of immunoprecipitates of detergent extracts from biosynthetically labelled M21 melanoma cells showed that MoAb 9.2.27 recognizes a 250 kilodalton (250K) molecule together with a high mol wt component (HMW-C), Mr greater than 500,000 dalton. Pulse-chase analysis of this antigen complex in extracts of 35S-methionine labelled cells, treated with either the monovalent ionophore monensin or endoglycosidase H, revealed that MoAb 9.2.27 recognizes the 250K N-linked glycoprotein in the absence of the HMW-C as well as several precursor glycoproteins ranging from 210-240K. The chondroitin sulfate nature of the HMW-C was indicated by its ability to label with 35S-sulfate ion and its sensitivity to beta elimination and proteoglycan-specific enzymes chondroitinase ABC and AC lya ses. MoAb F11 recognizes a glycoprotein of 100 kilodalton (100K) that has limited cell surface expression as it is secreted into spent culture media of melanoma cells. Pulse-chase analysis revealed the 100K antigen to be secreted at a slower rate than other major melanoma-associated glycoproteins, ie, fibronectin, suggesting a unique biosynthetic pathway. The 100K antigen is heavily glycosylated as evidenced by sensitivity to neuraminidase and biosynthetic alterations induced by monensin. Two monoclonal antibodies could thus be used effectively for an in depth study of biosynthetic and biochemical aspects of glyco-conjugated tumor associated antigens, paving the way for an analysis of their biological function in metastatic melanoma. (no Refs)

20. CYTOTOXIC T LYMPHOCYTES INDUCED BY SYNGENEIC MOUSE MELANOMA CELLS RECOGNIZE HUMAN MELANOMAS.

Wakabayashi S, Taniguchi M, Tokuhisa T, Tomioka H, Okamoto S
Dept. Dermatology, Sch. Medicine, Chiba Univ., Chiba, Japan
Nature; 294(5843):748-750 1981

Cytotoxic T lymphocytes (CTLs) against syngeneic B16 melanoma cells were induced in C57BL/6 mouse spleen cells cultured with mitomycin C-treated B16 cells. The CTLs killed cells of four human melanoma cell lines in addition to the syngeneic melanoma cells; the CTLs did not affect other mouse or human tumors. The T cells appeared to recognize melanoma-specific antigens rather than interspecies determinants of the major histocompatibility complex. C57BL/6 mice do not express I-E/I-C subregion gene products of the mouse H-2 complex that share cross-reactive determinants with human HLA-DR antigens. (14 Refs)

21. DOXORUBICIN CYTOTOXICITY ENHANCED BY LOCAL ANESTHETICS IN A HUMAN MELANOMA CELL LINE.

Chlebowski RT, Block JB, Cundiff D, Dietrich MF
Div. Medical Oncology, Dept. Medicine, Harbor-Univ. California Los Angeles Medical Center, 1000 W Carson St., Torrance, CA, 90509
Cancer Treat Rep; 66(1):121-125 1982

Local anesthetics may influence cell membrane structure and permeability. An established human melanoma cell line (SHG) derived from malignant ascites was used to evaluate the growth-inhibitory effects of local anesthetics (procaine and lidocaine) as well as of doxorubicin at incubation temperatures of 37.5 C and 40 C. In this system, procaine and lidocaine inhibited growth at 0.82 mg/ml and doxorubicin inhibited growth at 28 ng/ml. Noninhibitory concentrations of procaine (0.64 mg/ml) when combined with noninhibitory concentrations of doxorubicin (10 ng/ml) resulted in marked growth inhibition. Incubating temperatures of 40 C enhanced all effects or procaine and doxorubicin on cell growth. These results suggest that clinically achievable concentrations of local anesthetics enhance doxorubicin cytotoxicity. (Author abstract) (19 Refs)

22. BIOCHEMICAL AND IMMUNOLOGICAL CHARACTERIZATION OF CELLULAR DNA POLYMERASES ALPHA , BETA AND GAMMA, AND A REVERSE TRANSCRIPTASE FROM HUMAN MELANOMA TISSUE.

Chandra P, Balikcioglu S, Mildner B
Zentrum der Biologischen Chemie, Theodor-Stern-Kai 7, D-6 Frankfurt a. Main 70, W. Germany
Cell Mol Biol; 27(2/3):239-251 1981

The present study describes separation and purification of a reverse transcriptase and cellular DNA polymerases from human primary melanoma tissue. The specific requirements with respect to bivalent cations and template-primers for DNA polymerase alpha, DNA polymerase beta and DNA polymerase gamma, as well as for the reverse transcriptase, are reported. Sodium dodecylsulfate gel electrophoresis of the purified enzymes gave estimated values of mol wt of 160,000, 38,000, 100,000 and 68,000 daltons for DNA polymerase alpha, DNA polymerase beta, DNA polymerase gamma and reverse transcriptase respectively. Serological studies have shown that the reverse transcriptase of human melanoma tissue is not antigenically related to cellular DNA polymerase alpha, beta, or gamma, but is antigenically related to reverse transcriptases from baboon endogenous virus (BEV) and RD-114. This is the first human reverse transcriptase showing cross-reactivity to DNA polymerases from endogenous retroviruses. (Author abstract) (24 Refs)

23. NEUROHORMONAL AND CHEMOSENSITIVITY OF HUMAN MELANOMA COLONY FORMING UNITS IN SOFT AGAR (MEETING ABSTRACT).

Meyskens FL
University of Arizona, Tucson, AZ
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; :A20 1981

We measured the effect of a series of non-steroidal hormones (follicle stimulating hormone (FSH), luteinizing hormone (LH), melanocyte stimulating hormone (MSH), human chorionic gonadotropin (HCG), melatonin, nerve growth factor (NGF)) on human melanoma colony forming cells in soft agar from biopsies of 20 patients with metastatic melanoma. A complex array of responses were demonstrated, suggesting that a diversity of hormonal phenotypes are present. Melanoma colony forming units in soft agar from biopsies of 50 patients with metastatic melanoma demonstrated marked heterogeneity in chemosensitivity to nine chemotherapeutic drugs. Reduction in survival of colony forming units below 38% at one-tenth the pharmacologically achievable one hr concentration x time (our operational definition of chemosensitivity) was obtained in only 19% of 200 in vitro trials and was generally identical whether patients had been exposed to prior chemotherapy or not, suggesting that melanoma colony forming units are inherently resistant to presently available chemotherapeutic drugs. The soft agar assay was 86% accurate (25 of 29 cases) for identifying drugs to which the tumor was resistant in vivo and 63% accurate (12 or 19 trials) for identifyi ng drugs to which the tumor was clinically sensitive when mixed responses were included as responses. In contrast, if mixed responses were classified as progressive disease, then the accuracy for identifying sensitivity fell to 42% (8 of 19 trials). These investigations furnish a quantitative description of the chemosensitivity of human metastatic melanoma colony forming units and demonstrate that neurohormones can modulate melanoma colony forming units. Additionally, these studies can be regarded as a useful step towards the development of an in vitro chemosensitivity test for human melanoma and provide an operational quantitative basis for further exploration of in vitro directed therapy in metastatic neoplasms and classification of melanoma by neurohormonal responses. (no Refs)

24. VARIABILITY OF THE CELL SURFACE IN HUMAN MALIGNANT MELANOMA.

Hakim AA
Dept. Surgery, Oral Diagnosis, Physiology and Biophysics, Coll. Medicine, and Dentistry Univ. Illinois at Medical Center, Chicago, IL
Cell Mol Biol; 27(2/3):61-70 1981

Ten human malignant melanoma cell lines were examined for attachment to experimental substrates. The cell lines varied in their ability to attach to various substrates. Human fibroblast products or collagen-covered substratum enhanced cellular attachment, growth rate as monitored by 3H-thymidine uptake, collagen synthesis as monitored by 14C-proline incorporation, aggregation and development of tissue-like cell masses. Electron microscopic examination showed that cellular attachment correlates with the amounts of intracellular microfilaments. (Author abstract) (16 Refs)

25. GRANULAR BASAL CELL TUMORS IN THE SKIN OF THREE DOGS: A DISTINCT HISTOPATHOLOGIC ENTITY.

Seiler RJ
Dept. Pathology, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Vet Pathol; 19(1):23-29 1982

Granular cell variants of cutaneous basal cell tumors from three dogs are described. These tumors resemble a granular cell variant of basal cell tumor (carcinoma) in man. The tumors are characterized by classical basal cells as well as granular cells with numerous cytoplasmic granules. These granules are cytoplasmic vacuoles 0.3 um to 1.5 um that seem to be secondary lysosomes; they usually contain many small (42 nm), membrane-bound vesicles. No natural, non-neoplastic counterpart of these granular cells is known to exist in the skin, and the significance of the production and accumulation of the small vesicles is not known. The cytoplasmic granules, and their contents, resemble the granules of granular cell 'myoblastoma' although granular basal cells are of epithelial origin. (Author abstract) (25 Refs)

26. SIMILARITIES AND DIFFERENCES BETWEEN THE EFFECTS OF EPIDERMAL GROWTH FACTOR AND ROUS SARCOMA VIRUS.

Cooper JA, Hunter T
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
J Cell Biol; 91(3):878-883 1981

We have derived a line of A431 human tumor cells infected with Rous sarcoma virus (RSV). The infected cells contain the RSV-transforming protein, pp60src, which has characteristic tyrosine-specific protein kinase activity. As in other RSV-transformed cells, a 36,000-dalton protein is phosphorylated in RSV-infected A431 cells. Addition of epidermal growth factor (EGF) to the cells induces further phosphorylation of this protein. In contrast, this phosphoprotein is not detected in uninfected A431 cells, except when treated with EGF. Increased phosphorylation of the EGF receptor protein and of an 81,000-dalton cellular protein is dependent upon addition of EGF to the culture fluids, in both control and RSV-infected A431 cells. The results are discussed with reference to the similarities and differences between the tyrosine-specific protein kinases induced by RSV and activated by EGF. (Author abstract) (42 Refs)

REVIEWS

27. VON RECKLINGHAUSEN NEUROFIBROMATOSIS.

Riccardi VM
Baylor Neurofibromatosis Program, Dept. Medicine, Baylor Coll Medicine, Texas Medical Center, Houston, TX, 77030
N Engl J Med; 305(27):1617-1626 1981

Von Recklinghausen neurofibromatosis is reviewed, including clinical and laboratory features, natural history, pathogenesis, genetics, and management. Defining clinical features include multiple cafe au lait spots, multiple neurofibromas, and lisch nodules. Other common features include macrocephaly, CNS tumors, segmental hypertrophy, pseudarthrosis, short stature, and malignant disease. Laboratory diagnosis is not yet possible, but patients should undergo extensive evaluation to confirm the diagnosis, identify complications, and monitor progression. An increase in the size and number of hyperpigmented skin lesions and tumors is the common progression in neurofibromatosis. However, its extreme diversity precludes any other single natural history. The primary defect is thought to reside in the neural crest related secretory membrane system of the Golgi complex and endoplasmic reticulum, but no fully documented pathogenic schema have emerged to date. Genetic origin is an autosomal dominant mutation with a frequency of approx 1/3000. There are no apparent racial, ethnic, national, or sex restrictions. Management techniques include genetic counseling and timely surgery. Neurofibromatosis centers provide multidisciplinary teams for evaluation, follow up, therapy, feedback to private physicians, education, and counseling, and are important for proper patient care. (52 Refs)

28. MONOCLONAL ANTIBODIES SPECIFYING TUMOUR-ASSOCIATED ANTIGENS AND THEIR POTENTIAL FOR THERAPY.

Baldwin RW, Embleton MJ, Price MR
Cancer Res. Laboratories, Univ. Nottingham, Nottingham NG7 2RD, England
Mol Aspect Med; 4(5):329-368 1981

Technique for the production of monoclonal antibodies (MA) is described. A review of MA studies in animals is followed by personal experiences with the use of MA in human osteogenic sarcoma and malignant melanoma. Use of MA in other human tumors, as described in the literature, is discussed. In terms of therapy, MA has provided an alternative approach for selectively attacking malignant cells. Also discussed is the possibility of linking highly toxic substances to MA for therapy. The use of MA as carriers for chemotherapeutic agents is discussed. This approach to cytotoxic drug therapy is still new and many problems must be resolved. At present, there is as yet no conclusive evidence that the antigens specified by murine monoclonal antibodies on malignant melanoma, osteo-

genic sarcoma and colorectal carcinoma are recognized by patients. Nevertheless, MA specifying human tumor antigens, are providing new and exciting approaches for biochemically characterizing cell surface proteins and glycolipids. Other possible uses of the new technology are discussed. (97 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/117

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MELANOMA AND OTHER SKIN CANCER

Diagnosis, Treatment

SERIES CT22 No. 82/06

JUNE, 1982

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DIAGNOSIS

1. PROGNOSTIC FACTORS FOR MELANOMA PATIENTS WITH LESIONS 0.76-1.69 MM IN THICKNESS: AN APPRAISAL OF 'THIN' LEVEL IV LESIONS.

Day CL, Mihm MC, Sober AJ, Harris MN, Kopf AW, Fitzpatrick TB, Lew RA, Harrist TJ, Golomb FM, Postel A, Hennessey P, Gumport SL, Raker JW, Malt RA, Cosimi AB, Wood WC, Roses DF, Gorstein F, Rigel D, Friedman RJ, Mintzis MM
(c/o Sober) Dept. Dermatology, Massachusette General Hosp., Boston, MA, 02114

Ann Surg; 195(1):30-34 1982

Fourteen variables were tested for their prognostic usefulness in 203 patients with clinical Stage I melanoma and primary tumors 0.76-1.69 mm thick. Only two variables, primary tumor location and level of invasion, were useful in predicting death from melanoma for these patients. Of the 12 deaths from

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melanoma, 11 occurred in patients with primary tumors located on the upper back, posterior arm, posterior neck, and posterior scalp (= BANS). There has been only one death from melanoma in 136 patients with melanoma located at other sites (11/67 vs 1/136, p less than 0.0001 Fisher's Exact Test). Of the 67 BANS patients, 51 had Level II or Level III lesions and 5 (10%) died of melanoma. This compares with six deaths from melanoma in 16 patients (37.5%) with Level IV BANS lesions (5/51 vs 6/16, p = 0.01 Fisher Exact Test). The relatively high incidence of both melanoma deaths and regional node metastases for the BANS group merits consideration for testing the efficacy of elective regional node dissection for these patients. (Author abstract) (25 Refs)

2. A MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS FOR MELANOMA PATIENTS WITH LESIONS GREATER THAN OR EQUAL TO 3.65 MM IN THICKNESS. THE IMPORTANCE OF REVEALING ALTERNATIVE COX MODELS.

Day CL, Lew RA, Mihm MC, Sober AJ, Harris MN, Kopf AW, Fitzpatrick TB, Harrist TJ, Golomb FM, Postel A, Hennessey P, Gumport SL, Raker JW, Malt RA, Cosimi AB, Wood WC, Roses DF, Gorstein F, Rigel D, Friedman RJ, Mintzis MM, Grier RW
(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114
Ann Surg; 195(1):44-49 1982

Fourteen prognostic factors were examined in 79 patients with clinical Stage I melanoma greater than or equal to 3.65 mm in thickness. All nine patients with melanoma of the hands or feet died of melanoma. A Cox proportional hazards (multivariate) analysis of the remaining 70 patients showed that a combination of the following four variables best predicted bony or visceral metastases: (1) a nearly absent or minimal lymphocyte response at the base of tumor, (2) histologic type other than superficial spreading melanoma, (3) location on the trunk, and (4) positive nodes or no initial node dissection. Ulceration and/or ulceration width were not useful in predicting outcome either singly or in combination with other variables. Patients with negative lymph nodes and primary tumors of the trunk, hands, and feet did not do better than patients with positive nodes at those sites. Conversely, none of 16 patients with negative lymph nodes and extremity melanomas (excluding the hands and feet) or head and neck melanomas developed visceral or bony metastases (ie, 5-yr disease-free survival rate 100%). (Author abstract) (26 Refs)

3. PROGNOSTIC FACTORS FOR PATIENTS WITH CLINICAL STAGE I MELANOMA OF INTERMEDIATE THICKNESS (1.51-3.99 MM): A CONCEPTUAL MODEL FOR TUMOR GROWTH AND METASTASIS.

Day CL, Mihm MC, Lew RA, Harris MN, Kopf AW, Fitzpatrick TB, Harrist TJ, Golomb FM, Postel A, Hennessey P, Gumport SL, Raker JW, Malt RA, Cosimi AB, Wood WC, Roses DF, Gorstein F, Rigel D , Friedman RJ, Mintzis MM, Sober AJ
(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114
Ann Surg; 195(1):35-43 1982

Fourteen variables were tested for their ability to predict visceral or bony metastases in 177 patients with clinical Stage I melanoma of intermediate thickness (1.51-3.99 mm). A Cox multivariate analysis yielded a combination of four variables the best predicted bony or visceral metastases for these patients: (1) mitoses greater than 6/mm2 (p = 0.0007), (2) location other than the forearm or leg (p = 0.009), (3) ulceration width greater than 3 mm (p = 0.04), and (4) microscopic satellites (p = 0.05). The overall prognostic model chi square was 32.40 with four of freedom (p less than 10(-5)). Combinations of the above variables were used to separate these patients into at least two risk groups. The high risk patients had at least a 35% or greater chance of developing visceral metastases within 5 years, while the low risk group had greater than an 85% chance of being disease free at 5 years. Criteria for the high risk group were as follows: (1) mitoses greater than 6/mm2 in at least one area of the tumor, irrespective of primary tumor location, or (2) a melanoma located at some site other than the forearm or leg and histologic evidence in the primary tumor of either ulceration greater than 3 mm wide or microscopic satellites. The low risk group was defined as follows: (1) mitoses less than or equal to 6/mm2 and a location on the leg or forearm, or (2) mitoses less than or equal to 6/mm2 and the absence in histologic sections of the primary tumor of both microscopic satellites and ulceration greater than 3 mm wide. The number of patients in this series who did not undergo elective regional node dissection (N = 47) was probably too small to detect any benefit from this procedure. Based on survival rates from this and other studies, it is estimated that approximately 1,500 patients with clinical Stage I melanoma of intermediate thickness in each arm of a randomized clinical trial would be needed to detect an increase in survival rates from elective regional node dissection. (Author abstract) (40 Refs)

4. BASAL CELL EPITHELIOMA (CARCINOMA) IN CHILDREN AND TEENAGERS.

Rahbari H, Mehregan AH
Pinkus Dermatopathology Lab., 1314 N. Macomb St., PO Box 360, Monroe, MI, 48161
Cancer; 49(2):350-353 1982

Among over 390,000 routine dermatopathologic specimens there were 85 cases diagnosed as basal cell epithelioma (carcinoma) (BCE) in persons 19 yr old or younger. This number was refined to 40 cases de novo BCE in children and teenagers. Basal cell epithelioma unrelated to other conditions is rare in the young and it should be differentiated from similar fibroepithelial growths. (Author abstract) (19 Refs)

5. CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF GRANULAR CELL TUMORS IN THE AREA OF THE MOUTH, JAW, AND FACE.

Ploke G, Caselitz J, Maerker R
Nordwestdeutsche Kieferklinik der Universitat Hamburg, Martinistrasse 52, D-2000 Hamburg 20, W. Germany
Dtsch Zahnaerztl Z; 36(11):732-734 1981

Clinical and pathological findings in seven cases (4 males and 3 females, newborn up to 75 yr old) of granular cell tumors (GCT) of the orofacial area are reported. None of the patients had received prior treatment. Tumors were 0.5-3.0 cm in size. Two tumors were located on the skin; two were on the tongue; three were on the maxilla. Two maxillary tumors were congenital epulis. Tumors were tolerated or unnoticed for long periods because they were generally small and not painful. Diagnosis required differentiation from disorders such as fibroma, neurofibroma, papilloma, mucosal cysts, hyperplasias of secondary salivary glands, and malignant lymphoma. Laboratory findings were unexceptional. Therapy consisted of simple excision after intraoperative histologic examination. All tumors had indistinct borders lacking a capsule. Histologic examination showed round, oval, or elongated cell forms. Cell cytoplasm was eosinophilic or neutrophilic and contained PAS-positive granules. Carcinoembryonic antigen was detected by immunohistologic methods, suggesting that GCT does not originate from muscle cells, but may be related to perineural cells. No recurrence was noted during an observation period of 1-6 yr. (13 Refs) (In GER)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

6. THERAPY WITH BCG AND DNCB FOR MELANOMA AND NEVUS BASAL CELL EPITHELIOMA.

Lubbe D, Zaumseil RP, Gstottner R

Hautklinik des Bereichs Medizin, Martin-Luther-Universitat Halle-Wittenberg, Ernst-Kromayer-Strasse 5-8, DDR-4020 Halle, E. Germany

Dtsch Gesundheitswes; 36(44):1854-1859 1981

Primary therapy of melanomas and basal-cell epitheliomas is a surgical problem. Because curative surgery, particularly in cases of malignant melanoma, is not always possible, adjuvant therapies such as immunotherapy and chemoimmunotherapy have been used. In a controlled clinical study of 66 patients with malignant melanoma, no relevant differences could be seen between results of purely surgical treatment and those of surgery with adjuvant therapy during a 40-mo follow-up period. In individual cases (malignant melanoma and nevus basal-cell epithelioma) impressive local tumor remission was achieved in part by local DCNB therapy. Indications for routine immunotherapy must be worked out in scientific studies. (25 Refs) (In GER)

7. THE 'HOT SPLEEN' PHENOMENON IN METASTATIC MALIGNANT MELANOMA: ITS INCIDENCE AND RELATIONSHIP WITH THE IMMUNE SYSTEM.

Wagstaff J, Phadke K, Adam N, Thatcher N, Crowther D

Dept. Medical Oncology, Christie Hosp. and Holt Radium Inst., Wilmslow Road, Manchester, M2O 9BX, England

Cancer; 49(3):439-444 1982

Of patients with Stage II and III malignant melanoma, 34.7% display reversal of the liver-spleen ratio on technetium-99m-sulfur colloid isotope scans. Such an occurrence does not suggest a greater likelihood of relapse or a worse survival. The phenomenon is more common in female patients and there is a significant relationship between the presence of a 'hot spleen' and a high IgM level. Patients with Stage II disease and high IgM levels have relapses more quickly than do those with normal IgM levels. Lymphopenia is common in patients with Stage II and III disease and the survival of these patients is worse than that of those with normal lymphocyte counts. In this report, the data are discussed together with results from other investigations, and a unifying hypothesis is presented which explains the phenomenon and relates it to increased activity of macrophages as a result of the presence of the tumor. The usefulness of isotope liver scanning in Stage III malignant melanoma is also discussed. (Author abstract) (22 Refs)

8. DETECTION OF MELANOMA TUMOR ASSOCIATED ANTIGENS IN SERA BY ENZYME LINKED MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Hersey P, Schiltknecht E, Kemkemian H, McCarthy WH

No affiliation given

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

An enzyme linked immunosorbent assay (ELIZA) was developed for the detection of melanoma antigens in unfractionated or small mw fractions (less than 100,000d) of sera from melanoma patients. Antibodies were from 4 hybrid murine myelomas that were reported to be relatively specific for melanoma and to react with a high proportion of melanoma cells. In studies on 21 melanoma patients and 25 patients with various malignancies antigen was detected in a high proportion (95%) of the melanoma patients but in only 16% of non-melanoma patients. The studies on the small mw fraction of sera yielded the best discrimination between melanoma and non-melanoma patients. The reaction of the 4 monoclonals varied with sera from different patients suggesting they were detecting different but overlapping antigenic determinants. Levels of antigen in sera became undetectable after surgical removal of localized melanoma and recurrence of melanoma in one patient was preceded by the appearance of antigen in the sera by several mo. These results suggest that existing monoclonal antibodies to melanoma antigens may be useful to monitor tumor growth in melanoma patients and justify more extensive evaluation for this purpose. (no Refs)

9. SERUM HLA-A AND B ALLOANTIGENS IN PATIENTS WITH MALIGNANT MELANOMA.

Nathanson SD, Pellegrino MA, Ferrone S, Kobayashi H, Bonavida B, Ploegh

Div. Surgical Oncology, UCLA Sch. Medicine, Los Angeles, CA, 90024

Transplant Proc; 13(4):1939-1941 1981

Expressions of human WBC antigen (HLA)-A and B antigens in the sera of patients with melanoma and in autologous lymphocytes were compared and correlated with clinical stage of the disease. Forty-six of 111 melanoma patients (56 males, 55 females) and 8/29 normal controls expressed alien HLA-A and/or B antigens in their sera in addition to the appropriate autologous antigens. Alien antigens were found in 18/49 Stage I patients, 9/28 Stage II, and 19/34 Stage III. HLA-B5, the most commonly encountered alien antigen, was found in 7/49 Stage I patients, 4/28 Stage II, and 10/34 Stage III patients. Stage III melanoma patients expressed HLA-B5 significantly more often than did controls. No concomitant increase in HLA-B5 expression on lymphocytes was observed. Alien HLA-B12 was found in the sera of 4/49 Stage I patients, 2/28 Stage II, 7/34 Stage III, and 1/29 controls. The remaining alien antigens in the sera of melanoma patients and controls consisted of HLA-A2, 3, 9, and 10, and HLA-B7 and 17. HLA antigens in serial sequential serum samples of 4/5 selected patients did not vary from the first sample; one patient developed an additional HLA-A9 when liver metastases appeared. Three of the five patients had alien HLA-B5 in their sera throughout the course of the disease. Alien HLA antigens of recoded serum samples of 21 selected patients did not vary from the first study. (16 Refs)

CHEMOTHERAPY

10. CHEMOTHERAPY OF MALIGNANT MELANOMA.

Jehn U, Wilmanns W
Medizinische Klinik III, Klinikum Grosshadern der Universitat, Marchioninistr. 15, D-8000 Munchen 70, W. Germany

MMW; 123(50):1945-1948 1981

The status of chemotherapy (CT) of malignant melanoma (MM) is reviewed. CT as palliative therapy is indicated only for Stage III disease. Characteristics of MM such as a doubling time of 7 wk, mean generation time of 3 days, and an S-phase duration of 20 hr suggest that MM should be sensitive to CT. Interpretation of data is difficult, however, because many reports concentrate on the properties of new medications, rather than on the characteristics of MM. Many studies do not use common standards for measuring tumor response (greater than 50% or greater than 25% tumor regression). Agents tested in monochemotherapy include alkylating agents, antimetabolites, antibiotics, vinca alkaloids, and other agents. Of these, only the alkylating agent ifosfamide, the antibiotic actinomycin D, the vinca alkaloid vindesine, and dacarbazine have produced significant results. Comparisons of data from various studies are difficult, because differences in administration schemes, male and female metabolism, tumor localization, and patient selection have not been taken into account. Favorable results have been achieved with two chemotherapeutic drugs including cisplatinum, and also with three, four, and five chemotherapeutic drugs, but ap parent improvement in patient survival time may be due to exclusion of certain patient categories from evaluation. Review of data suggests that claims of significant response to CT must be examined carefully. (27 Refs) (In GER)

11. A MULTICENTRE PHASE II STUDY OF VINDESINE IN MALIGNANT MELANOMA (MEETING ABSTRACT).

Carmichael J, Smyth J, Calman K, Mackie R, Atkinson R
University of Edinburgh, Edinburgh, Scotland

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Thirty-eight patients with advanced malignant melanoma were treated with Vindesine (VDS) 3 mg/M2 iv weekly for a minimum of 6 wk. The median age of patients was 54 yr and 24 were female. Six patients were unevaluable, 5 dying within 3 wk of progressive disease and 1 developing jaundice following 2 treatments. Of 32 assessable patients, 14 had received prior chemotherapy, 11 with dacarbazine (DTIC) either alone or in combination. Four complete responses in nodal or soft tissue disease and 5 partial responses were observed, producing an overall response rate of 28%. Of the complete responses 3 remain in remission at 52, 20 and 6 wk respectively; the other patient relapsed at 16 wk and following a further partial response to VDS died 62 wk after the initiation of therapy. Overall toxicity was mild. Anemia was common though transfusion was required in only 1 case. Moderate leukopenia was seen in 19% of patients. Thrombocytopenia was not observed. Neurological toxicity was seen in 25% of patients and was predominantly sensory. Significant but reversible motor impairment was seen in 2 patients. Mild gastrointestinal symptoms were seen in 25% of patients and phlebitis at the injection site in 4 cases. These results suggest that Vindesine has definite activity in malignant melanoma capable of producing complete responses. The drug is well tolerated by the majority of patients. (no Refs)

12. EORTC PHASE II STUDY OF VINDESINE (VDS) IN ADVANCED MELANOMA (MEETING ABSTRACT).

Rumke P, Everall JD, Mulder J, Rozencweig M, Czarnetzki B, Thomas D
No affiliation given

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In a phase II cooperative study conducted in 1979 and early 1980, in which 5 institutions participated, VDS as a single agent (weekly iv bolus injections of 2-3 mg/m2 during 6 wk and once in 2-3 wk thereafter) was given to 23 eligible patients (pts) with advanced melanoma. Excluding one case of early death 22 pts (13 male, 9 female) were evaluable. Ages were 28-76 yr (median 51 yr) and the Karnofsky performance status at entry ranged from 40-100 (median of 80). Prior chemotherapy was received by 15 pts (6 only dacarbazine, 2 only N-Phosphonoacetyl-L-aspartate (PALA) 1 DTIC + lomustine (CCNU), 6 various c ombinations of which 5 included vincristine). Sixteen pts received initially 3 mg/m2, dose reduction and/or postponement of injections took place in 5 of them due to leukopenia and neurotoxicity including sub-ileus. Six pts received initially 2-2.8 mg/m2 and in one receiving 2.8 mg/m2 the last dose had to be reduced and postponed. Three to 14 injections (median 6) were administered. Toxicity concerned: paresthesia mild 5, moderate 4, severe 2, neurological not specified 6, sub-ileus 1, anorexia mild 4, moderate 1, nausea/vomiting mild 3, moderate 1, diarrhea 1, fatigue moderate 1, severe 2, fever 3, genitourinal incontinence severe 1, alopecia mild 1, moderate 6, severe 2, leucopenia less than 4 greater than 2 x 10(3)/mm3 11, less than 2 x 10(3)/mm3 5 pts. The nadirs of WBC counts were 0.6-3.9 x 10(3)/mm3 (median 3.0). Principal metastases were in: skin 11, lymphnodes 8, liver 6, lung 5, brain 1 pts. Treatment results: Progression of disease in 21 pts, no change in 1 pt. The latter was a male of 31 who had one in transit skin and one lymph-node metastasis. He received 14 injections of 2 mg/m2 during 3 1/2 mo while the lymph-node metastasis regressed slightly and the skin metastases remained the same. Two mo-after arbitrary discontinuation of VDS the disease progressed. Conclusion; the effect of VDS as a single agent in advanced melanoma is negligible. (no Refs)

13. COMBINATION CHEMOTHERAPY WITH CISPLATIN (C) AND VINDESINE (V) IN ADVANCED MALIGNANT MELANOMA (MEETING ABSTRACT).

Dodion P, Mulder M, Cavalli F, Czarnetzki B, Thomas D, Rozencweig M
No affiliation given

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In an ongoing nonrandomized cooperative trial, 35 eligible patients with advanced malignant melanoma have received a combination chemotherapy regimen consisting of C 100 mg/m2 as a 24 hr infusion on d 1 and V 3 mg/m2 iv bolus on d 1, 8, 15. Courses are repeated every 4 wk. Doses are reduced according to myelosuppression, gastrointestinal intolerance, renal and neurological toxicities. Among 19 currently evaluable patients, there are 10 men and 9 women. Their median age is 52 yr (28-65), the median performance status is 100 (60-100). All have had prior surgery, three have had prior radiotherapy and 12 have received prior chemotherapy with single agents. All but one have metastatic disease; 10 patients have soft tissue disease only, and 9 have visceral involvement. Complete remission (CR) has been achieved in one patient and partial remission greater than 50% (PR) in six patients for an overall response rate of 37%. The CR is still lasting after 9 mo; the median duration of PR has not yet been reached but will be in excess of 11.5 wk. Response rate seems to be independent of performance status, sex, prior chemotherapy and visceral involvement. Leukopenia has been more frequent than thrombocytopenia. WBC less than 4000/mm3 have been noted in 12 patients, four of these have had WBC less than 2000/mm3. Platelets less than 100,000/mm3 have been encountered in two patients only. Nausea and vomiting have been universal and severe in one third of the patients. Other toxic effects include alopecia (14), neurological manifestations (7), myalgias (3), renal impairment (3), diarrhea (2), mucositis (2), and hearing loss (1). (no Refs)

14. CHEMOIMMUNOTHERAPY OF MALIGNANT MELANOMA (MM) WITH DTIC, ACNU, VCR AND OK432 (MEETING ABSTRACT).

Jimbow K, Nishio C
Department of Dermatology, Sapporo Medical College, Sapporo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Clinical and histopathological evaluation of MM was done to 85 cases, who had been registered and treated in our clinic since 1976, with respect to the stages of MM involvement and effect of chemotherapy with or without OK432. The most common form was the 'acrolentiginous mucosal type' which comprised more than 50-60% of total cases in both male and female. A significant improvement in survival rate was obtained in the group treated by chemoimmunotherapy of dacarbazine (DTIC), nimustine (ACNU), Vincristine (VCR) with OK432. In several cases, a complete response for more than 6 mo was noted in metastatic lesions of skin, brain and lung. Thus, the combination therapy of DTIC, ACNU, VCR and OK432 appears to be encouraged. (no Refs)

15. A PHASE II STUDY OF BLEOMYCIN, ONCOVIN, LOMUSTINE AND DTIC (BOLD) IN DISSEMINATED MELANOMA (MEETING ABSTRACT).

Jose DG, Minty CM, Hillcoat B
Peter MacCallum Hospital, Melbourne, Australia
Clinical Oncology Society of Australia, November 24-27, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Sixteen consecutive patients with metastatic stage 4 melanoma who had not previously received chemotherapy were treated with BOLD protocol. Drugs given were bleomycin 15 mg i/V days 1 and 4, 4 weekly (to maximum total dose of 350 mg), oncovin (vincristine) 1 mg/m2 (maximum single dose 2 mg) i/V on days 1 and 5, 4 weekly, lomustine (CCNU) 80 mg/m2 orally 6 weekly and dacarbazine (DTIC) 200 mg/m2, i/V on days 1-5, 4 weekly. Patients entered had measurable visceral metastases, or massive inoperable deposits of melanoma at any site, were less than 70 yr, free of major organ dysfunction, and a life expectancy greater than 2 mo. Thirteen evaluable patients were those who received two or more courses of BOLD treatment. Five patients (38%) had partial response, 4 (28%) had stabilization of disease for 3 mo and 4 (28%) had progressive disease. Overall median survival is 28 wk with 5 patients still in remission and 12 still alive. Median survival among 9 responders is 37 wk while those 4 whose disease progressed is 15 wk. Toxicity of BOLD regime required dose modification for vomiting, neurotoxicity, and thrombocytopenia. Overall patient acceptance was good. This small study confirms that BOLD is an effective palliative treatment for metastatic melanoma with tumor response in half the patients and prolongation of survival with mild to moderate toxicity. (no Refs)

16. METASTATIC TUMOR TO THE RETINA AND VITREOUS CAVITY FROM PRIMARY MELANOMA OF THE SKIN: TREATMENT WITH SYSTEMIC AND SUBCONJUNCTIVAL CHEMOTHERAPY.

Robertson DM, Wilkinson CP, Murray JL, Gordy DD
Dept. Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, MN, 55901
Ophthalmology (Rochester); 88(12):1296-1301 1981

The cases of two female patients (37 and 43 yr old) who had symptoms of vitreous floaters related to metastatic melanoma cells arising from primary skin melanoma treated several years previously are described. Histocytologic diagnosis and management with systemic and subconjunctival chemotherapy are detailed. Each patient initially had 20/20 central visual acuity in both eyes; numerous unusual golden brown cellular aggregates were evident upon slit-lamp observation. The elder woman was treated with oral doses of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, but malignant cells proliferated. Subconjunctival 5-(3,3-dimethyl-1-triazene) imidazol-4-carboxamide injections, 1.5 mg active compound every 3 days for a total of five doses, plus several series of 400 mg iv daily, were administered but failed to halt metastasis. The second patient exhibited decline in left-eye visual acuity to 20/30 after 6 mo and had greatly increased numbers of pigmented cells within the vitreous. Systemic 1-3-bis(2-chlorethyl)-1-nitrosourea (BCNU) and subconjunctival injections of 0.5 mg of BCNU every 3 days for a total of six doses were administered. Progressive neovascular glaucoma led to the need for enucleation after 5 mo. Treatment in the cases may have failed as a result of insufficient active ingredient. Subconjunctival injections were well tolerated, suggesting that a more aggressive chemotherapy schedule could have been attempted. (10 Refs)

RADIOTHERAPY

17. RADIOTHERAPY OF METASTATIC MELANOMAS.

von Lieven H, Lissner J
Radiologische Klinik der Universitat, Ziemenstr. 1, D-8000 Munchen 2, W. Germany
MMW; 123(50):1941-1944 1981

Applications of radiotherapy (RT) in the treatment of metastatic melanoma (MM) are described based on a retrospective study of 67 patients. MM was histologically confirmed in all patients; no patients had undergone prior surgery or RT. Lymph node metastases were irradiated with Co60 gamma rays. Primary tumors were irradiated with fast electrons. A total dose of 23.5-86.0 Gray was delivered in fractions of 2.5-4.3 Gray. Freedom from recurrence was achieved at a rate dependent on total dose and duration of treatment. Results indicate that the radiosensitivity of MM is less than that of other skin tumors but comparable to that of tumors of other organs. For a total dose of 55.0-70.0 Gray, a weekly dose of 10-12 Gray is recommended. Fourteen patients with Stage I disease received prophylactic RT of regional lymph nodes; and only 2 patients developed regional metastases. No recurrences were found after doses over 1600 rad equivalent therapy. RT produced results at least comparable to those from lymphadenectomy in cases of occult metastases. For cases with manifest lymph node metastases a combination of RT and lymphadenectomy is recommended. Palliative RT of distant metastases achieved relief of symptoms in most cases with a dose of 50 Gray in 5 wk. Side effects of RT included sc fibrosis and radiogenic ulceration. The risk of ulceration was particularly high in the lower extremities of patients with circulatory disorders. Overall results indicate the value of RT in curative or palliative therapy of MM. (21 Refs) (In GER)

18. LASER RADIATION THERAPY OF SKIN MELANOMA.

Wagner RI, Kozlov AP, Moskalik KG
Petrov Res. Inst. Oncology, Leningradskaya-Str. 68, Pevochny 2, 188646 Leningrad, USSR
Strahlentherapie; 157(10):670-672 1981

Pulsed neodymium laser radiation was used for the treatment of 79 patients with cutaneous melanomas and 19 patients with melanoma metastases to the skin. The patients were followed up from 3 months up to 8 years. During this period local recurrences were detected in two cases. Out of 70 patients with cutaneous melanomas, who by the start of the treatment had no metastases in the regional lymph nodes or distant organs, metastases developed in 15 patients (21.4%). There are all reasons to considered pulsed laser radiation an effective means of treatment of some forms of skin melanoma. (Author abstract) (8 Refs)

19. PROTON-BEAM IRRADIATED EPITHELIOID CELL MELANOMA OF THE CILIARY BODY.

Zinn KM, Stein/Pokorny K, Jakobiec FA, Friedman AH, Gragoudas ES, Ritch R
(c/o Jakobiec), Manhattan Eye, Ear and Throat Hosp., 210 East 64th St., New York, NY, 10021
Ophthalmology (Rochester); 88(12):1315-1321 1981

An attempt was made to use cyclotron-generated proton-beam irradiation in a case of ciliary body melanoma of the left eye in a 25-yr-old Caucasian male. Approx 1 yr after treatment, vision had deteriorated badly and the tumor was apparently enlarging. Enucleation was performed; the results of gross, photomicrographic, and electron micrographic examination of the eye are reported. Some degeneration of tumor cells was evident, and tumor capillaries had thickened basement membranes and perivascular fibrin deposition. A rare leptomeric structure which is apparently a modification of cytoplasmic filaments was discovered. Radiotherapy had evidently affected tumor growth but not sufficiently to arrest growth or cause necrosis of the tumor. (36 Refs)

SURGERY

20. ADJUVANT CRYOTHERAPY FOR FOCAL NODULAR MELANOMA OF THE CONJUNCTIVA.

Jakobiec FA, Brownstein S, Wilkinson RD, Katzin HM
(c/o Brownstein) Dept. Ophthalmology, Royal Victoria Hosp., Room E4.61, 687 Pine Ave. W., Montreal, Quebec H3A 1A1, Canada
Arch Ophthalmol; 100(1):115-118 1982

After excision of invasive conjunctival melanoma, there is a high recurrence rate, usually owing to small amounts of residual intraepithelial melanocytes or tumor cells at the base of the excision. Adjuvant cryotherapy was used in two patients to widen the margins of surgical excision and prevent recurrences, which have not developed during periods of 28 and 24 months postoperatively. This method allows preservation of substantia propria and reduces possible functional complications from surgical sacrifice of larger amounts of full-thickness conjunctiva. (Author abstract) (9 Refs)

OTHER THERAPEUTIC MODALITIES

21. CLINICAL HYPERTHERMIA: RESULTS OF A PHASE I TRIAL EMPLOYING HYPERTHERMIA ALONE OR IN COMBINATION WITH EXTERNAL BEAM OR INTERSTITIAL RADIOTHERAPY.

Manning MR, Cetas TC, Miller RC, Oleson JR, Connor WG, Gerner EW
Radiation Oncology Div., Univ. Arizona Health Sciences Center, Tucson, AZ, 85724
Cancer; 49(2):205-216 1982

Forty-three patients with advanced, locally accessible neoplasms were treated in a Phase I clinical trial employing hyperthermia alone or hyperthermia combined with either high-dose-rate external beam or low-dose-rate interstitial radiotherapy (interstitial thermoradiotherapy). All patients had failed previous conventional therapeutic attempts, including various combinations of surgery, chemotherapy and radiation therapy. A number of tumors with different histologies were treated, including squamous cell carcinoma, adenocarcinoma, melanoma, malignant fibrous histiocytoma, and sarcoma. The response evaluation criteria used included no response (NR- less than 50% decrease in tumor vol), partial response (PR-50% less than or equal to tumor vol reduction less than 100%) and complete response (CR-complete tumor disappearance). For all tumor types, hyperthermia therapy alone resulted in a total response rate of 45% (27% PR, 18% CR). Hyperthermia combined with high-dose-rate external beam radiotherapy yielded a total response rate of 80% (53% PR, 27% CR). Seventeen patients treated with interstitial thermoradiotherapy displayed a 100% total response rate (29% PR, 71% CR). By tumor histologies for all treatment groups, total response rates have ranged from 50 to 79% for all types except melanoma, which has shown a 100% (8/8) response rate to date. Response durations have varied from 1 to 24 mo. Twelve of the 43 patients remain alive; 3 have no evidence of disease (NED) while 9 have either stable local disease or are NED in the treated vol but have metastatic disease. Complications have been minimal. The results of this Phase I trial demonstrate that hyperthermia alone or combined with radiation can be safely applied in the treatment of malignant disease. Most importantly, the data suggest that hyperthermia, especially when combined with interstitial thermoradiotherapy, can yield remarkable results in the eradication of local cancers. (35 Refs)

22. RESPONSE OF HUMAN MALIGNANT MELANOMA XENOGRAFTS TO HYPERTHERMIA: EFFECT OF VASCULAR OCCLUSION.

Rofstad EK, Brustad T
Norsk Hydro's Inst. Cancer Res., Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Int J Radiat Oncol Biol Phys; 7(12):1685-1687 1981

Single-cell survival of human malignant melanoma (MM) xenografts after hyperthermic treatment under normal and hypoxic conditions was assayed. E.E. MM (EE) cells were obtained from an axillary lymph node metastasis in a 62-yr-old man. V.N. melanoma (VN) cells were obtained from an sc metastasis in a 29-yr-old woman. NMRI/nu/nu/Han mice (males and females) received flank transplants of tumor from passages 30-35 of EE or passages 20-25 of VN melanoma. Treatments were performed when tumors reached a diameter of 8-12 mm. Tumors were exposed to hyperthermia (42.5 C) by immersion in a water bath for varying times. Blood supply to some tumors was occluded by application of a tourniquet 15 min before immersion. Hyperthermia reduced the colony-forming capacity of MM cells on soft agar. VN cells were more sensitive than EE cells. Heat sensitivity of both cell types was greatly increased by occlusion of the tumor blood supply before treatment. Temperatures of clamped and nonclamped tumors were the same, indicating that reduced cell survival in clamped tumors was not due to higher temperatures. Slope (D0) values were calculated for exponential plots of cell survival versus time. The ratios of D0 for unclamped tumors to D0 for clamped tumors were 6.6 +-3.6 for EE cells and 2.3 +-0.5 for VN cells. (19 Refs)

CASE REPORTS

23. TUMOR CONFERENCE 39. MALIGNANT MELANOMA OF LIPS AND HARD PALATE.

Bart RS, Kopf AW
Oncology Section, Skin and Cancer Unit, New York Univ. Medical Center, New York, NY
J Dermatol Surg Oncol; 7(12):965-970 1981

The case of a 71-yr-old woman with malignant melanoma of the lips and hard palate is presented. Histological examination of biopsy specimens showed single and clustered atypical melanocytes, numerous melanophages, and a sparse inflammatory infiltrate. These findings were interpreted as lentigo maligna melanoma. The patient underwent excision of the involved mucous membrane from the hard palate, excision of the pigmented area on the alveolar ridge, wedge resection of the lower lip, and a lip-shave procedure with mucosal advancement. The pigmented areas on the upper lip were treated with cryosurgery. (10 Refs)

24. VITILIGO OR HALO NEVI OCCURRING IN TWO PATIENTS WITH CHOROIDAL MELANOMA.

Albert DM, Todes-Taylor N, Wagoner M, Nordlund JJ, Lerner AB
Dept. Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA, 02114
Arch Dermatol; 118(1):34-36 1982

Vitiligo frequently develops in patients with cutaneous melanomas, especially those who have survived with metastases for prolonged periods. To our knowledge, only one patient with an ocular melanoma in whom vitiligo developed has been described. We have observed a second patient in whom vitiligo developed 6 to 8 years after he had undergone an enucleation for ocular melanoma. Multiple halo nevi developed in a third patient who had an ocular melanoma. The association of vitiligo and ocular melanomas in these patients may not be the result of chance alone. (Author abstract) (15 Refs)

25. SYRINGOCYSTADENOMA PAPILLIFERUM OF THE EYELID.

Jakobiec FA, Streeten BW, Iwamoto T, Harrison W, Smith B
Manhattan Eye, Ear and Throat Hosp., 210 East 64th St., New York, NY, 10021
Ophthalmology (Rochester); 88(12):1175-1181 1981

Clinical and pathologic characteristics of slowly developing hyperkeratotic lesions removed from the eyelid margins of two white men (41 and 34 yr old) are described and illustrated with photomicrographs. Upon excision the tumors were identified as syringocystadenoma papilliferum, a benign adnexal tumor not well described in the literature. Transmission electron microscopy (TEM) of formalin-fixed wet tissue made evident the two types of lumen-forming cells, basaloid cells and plasma-forming cells, from the case of the older man. Results of transmission electron microscopy support an apocrine theory of histogenesis for syringocystadenoma papilliferum. One luminal cell had numerous mitochondria; much amorphous cellular debris within many lumens was noted. Both patients had lesions located at lid margins where only the apocrine glands of Moll are found, and in the second case large apocrine cysts were associated with the lesion. (14 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

26. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.

Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981

Patterns of occurrence and possible causative factors in cutaneous malignant melanoma (MM) are reviewed. MM occurs in 1.8-28.57/100,000 persons, depending on the geographical area studied. A world-wide increase in incidence has been reported with rates increasing as much as 340% in 12 yr. MM occurs most frequently during middle age. Women are affected approx twice as often as men. Survival time after diagnosis is longer for women, however; this may be because MM of the trunk occurs most often in men. Approx 40% of MM carry estrogen receptors, suggesting that hormonal influences affect the incidence and progression of the disease. Avoidance of pregnancy and hormonal contraceptives is therefore recommended for women with MM. Approx 1-7% of MM are related to an autosomal dominant or polygenic factors. In precursor mole syndrome atypical nevi become transformed into MM. A few cases of MM occurring in married couples have been reported that may be due either to infectious factors or to similarities in lifestyle. Ethnic and racial factors affect MM incidence; Celtic or Nordic types showing the highest incidence. Exposure to UV radiation has not been ruled out as a causative factor. Occurrence of MM in locations protected from sunlight suggests that a circulating factor is involved in tumor induction, but no such factor has been demonstrated. (65 Refs) (In GER)

27. EPIDEMIOLOGIC ASPECTS OF THE CURRENT OUTBREAK OF KAPOSI'S SARCOMA AND OPPORTUNISTIC INFECTIONS.

CDC Task Force on Kaposi's Sarcoma and Opportunistic Infections (c/o J. Curran) Technical Information Services, Centers for Disease Control, Atlanta, GA, 30333
N Engl J Med; 306(4):248-252 1982

Surveillance activities and current epidemiologic knowledge of the recent outbreak of Kaposi's sarcoma and opportunistic infections among homosexual men in the United States are described. During the period June 1-November 10, 1981, 159 cases of Kaposi's sarcoma, Pneumocystis carinii pneumonia, and other opportunistic infections in persons less than 60 yr old were reported to the Centers for Disease Control. Among 76 men with P. carinii pneumonia, 30 died of the initial infection. Of 46 survivors, 13 subsequently died, including 4/8 who had recurrent P. carinii pneumonia. The remaining deaths were attributed to Kaposi's sarcoma or to other opportunistic infections. Among 15 patients with both Kaposi's sarcoma and P. carinii pneumonia, Kaposi's sarcoma was diagnosed first in 6, pneumonia was diagnosed first in 6, and the diagnoses were simultaneous in 3. Of 10 patients with other serious opportunistic infections, 4 had progressive or disseminated herpes simplex virus infections. Over 40% of patients with Kaposi's sarcoma, P. carinii pneumonia, or both had other serious opportunistic infections. A secular increase in the number of reported cases was observed. All but one of the 159 cases occurred in men, 92% of whom were reported to be homosexual or bisexual. Over 75% of patients lived in New York City, San Francisco, or Los Angeles. (25 Refs)

28. UNDERSTANDING PATIENT DELAY IN MALIGNANT MELANOMA: IMPLICATIONS FOR EDUCATION (MEETING ABSTRACT).

DiClemente RJ, Bandyk MG, Ehlke GA
Division of Resources, Centers, and Community Activities, National Cancer Institute, Bethesda, MD
Proceedings of the 15th Annual Meeting of the American Association for Cancer Education, November 11-14, 1981, San Diego, California. The Association 73 pp., 1981.

Malignant melanoma is rapidly becoming a major public health problem. The incidence of melanoma is rising at an annual rate of approx six percent, second only to lung cancer in women. Early detection and prompt surgical treatment offer a favorable prognosis in melanoma. Unfortunately, there is some evidence to indicate that patients delay in seeking medical advice. This delay contributes to further tumor advancement which may lead to an unfavorable prognosis. The objective of the NCI Melanoma Lagtime Study is to develop a model which may lead to an unfavorable prognosis. The objective of the NCI Melanoma Lagtime Study is to develop a model which could explain patient delay based on information about the relationship between psychosocial and demographic characteristics of the patient and the pathological and clinical characteristics of melanoma. Emphasis will be placed on identifying those variables which have been demonstrated to be significantly related to patient delay. This model explaining patient delay may suggest associations between delay and inadequate education. If appropriate, recommendations would be made to incorporate new insights into the planning, development and implementation of public health education programs aimed at increasing awareness of the signs and symptoms of melanoma, and encouraging utilization of medical services during the early stages of the cancer. (no Refs)

SELECTED PRECLINICAL STUDIES

29. CLONAL CHARACTERISTICS OF CUTANEOUS T CELL LYMPHOMAS: CYTOGENETIC EVIDENCE FROM BLOOD, LYMPH NODES, AND SKIN.

Nowell PC, Finan JB, Vonderheid EC
Dept. Pathology/G3, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
J Invest Dermatol; 78(1):69-75 1982

Chromosome studies were done on mitogen-stimulated lymphocytes from one or more tissues (blood, lymph nodes, skin lesions) in 15 patients with mycosis fungoides or Sezary syndrome. A cytogenetically abnormal clone was found in 10 individuals, including 6 with data from several tissues. In four cases the same aberrant clone was identified in a skin lesion as well as in blood and/or lymph node. the abnormal chromosome patterns ranged from hypodiploid to hypertetraploid, and there was no evidence of unrelated karyotypically-altered lines at different sites. A 6q- chromosome, previously reported in acute lymphocytic leukemia, was found in two patients. The results support the concept that cutaneous T cell lymphomas (CTCL) are clonal disorders, presumably unifocal in origin, with the skin lesions populated by cells from the same neoplastic clone that involves lymph nodes and blood. (Author abstract) (17 Refs)

30. MELPHALAN PREVENTS THE FORMATION OF DOUBLE-STRANDED DNA REPLICATION INTERMEDIATES IN HUMAN MALIGNANT MELANOMA CELLS.

Lonn U, Lonn S
Dept. Histology, Karolinska Institutet, P.O. Box 60400, S-104 01 Stockholm, Sweden
Carcinogenesis; 2(12):1311-1316 1981

When human melanoma cells are lysed in a neutral buffer they release from the chromosomes double-stranded DNA replication intermediates. We have now examined the effect of a bifunctional alkylator (melphalan) on the formation of these intermediates. After treatment for 25 min there is little or no release of double-stranded DNA intermediates from the chromosomes. When the cells are washed free of the drug and cultivated further there is a resumed formation of the DNA intermediates. This is paralleled by the finding that the cells, when the drug is removed, after a time-lag, regain the capacity to proliferate. (Author abstract) (7 Refs)

31. IMMUNIZATION OF SYNGENEIC MICE AGAINST MALIGNANT MELANOMA WITH SUBCELLULAR MEMBRANE FRACTIONS OF A BROMODEOXYURIDINE-GROWN VARIANT.

Weintraub SB, Calvelli TA, Silagi S
(c/o Silagi) Dept. Obstetrics and Gynecology, Cornell Univ. Medical Coll., 515 East 71st St., New York, NY, 10021
Cancer Immunol Immunother; 12(1):63-70 1981

In vivo tumor rejection activity (without adjuvant) of subcellular membrane fractions (CM) isolated from a non-tumorigenic mouse melanoma variant was examined. The C3471 variant line originated by continuous growth of tumorigenic B559 line in the presence of thymidine analog 5-bromodeoxyuridine. Immunization with CM from C3471 cells provided effective prophylaxis against formation of lethal B559 melanomas in challenged C57BL/6 mice; plasma membrane vesicles also provided immunization. Immunization with intact C3741 cells yielded more efficient rejection of B559 melanoma than did immunization with CM. CM of B559 cells were not immunogenic, although the latency period was approx doubled compared to controls. Normal intact, viable primary fascia cells and membranes from C57BL/6 mice had no immunogenic value. Mice immunized with intact C3471 cells could reject challenge by either in vivo-tumor derived or cultured B559 cells. Inoculation of spleen cells and peritoneal exudate cells from C3471 CM-immunized mice in Winn assays neutralized malignant properties of B559 melanoma cells in a dose-responsive way, indicating that the syngeneic host response elicited by CM of C3471 cells is cell-mediated. (44 Refs)

32. ENHANCED EXPRESSION OF MELANOMA-ASSOCIATED ANTIGENS AND BETA2-MICROGLOBULIN ON CULTURED HUMAN MELANOMA CELLS BY INTERFERON.

Liao SK, Kwong PC, Khosravi M, Dent PB
Dept. Pathology, Health Sciences Centre, McMaster Univ., 1200 Main St. West, Hamilton, Ontario L8N 3Z5, Canada
JNCI; 68(1):19-25 1982

The effect of human leukocyte interferon (IFN) on the in vitro growth and expression of melanoma-associated antigens (MAA), beta2-microglobulin (beta2m) and HLA-DR antigen on cultured human melanoma cells was studied. Exposure of melanoma cells to IFN for 64 hours resulted in a dose-dependent inhibition of growth with 46% reduction in cell number at 10(3) U IFN/ml and 74% reduction at 10(5) U/ml. Quantitative absorption experiments in the mixed hemadsorption assay determined that the expression of MAA and beta2m on treated cells was enhanced at 10(2) -10(5) U IFN/ml, twofold to fivefold for MAA and fivefold to twelvefold for beta2m. No change was seen in HLA-DR antigen expression. The IFN-induced enhancement of MAA and beta2m could be detected as early as after 16 hours and a maximum expression was reached at 96 hours after IFN exposure. The IFN-induced enhancement of MAA and beta2m on melanoma cells was reversible. Studies with melanoma cells grown in stationary phase and serum-deprived conditions indicated that IFN-induced augmentation of MAA and beta2m did not require cell proliferation. The data suggest that the effect of IFN on antigen expression is independent of its effect on cell growth. Further studies are needed to fully elucidate the mechanism. (Author abstract) (42 Refs)

33. CHARACTERIZATION OF STRUCTURAL PROPERTIES FOR MORPHOLOGICAL DIFFERENTIATION OF MELANOSOMES: II. ELECTRON MICROSCOPIC AND SDS-PAGE COMPARISON OF MELANOSOMAL MATRIX PROTEINS IN B16 AND HARDING PASSEY MELANOMAS.

Jimbow K, Jimbow M, Chiba M
Dept. Dermatology, Sapporo Medical Coll., Minami 1, Nishi 16, Sapporo 060, Japan
J Invest Dermatol; 78(1):76-81 1982

This study compared the qualitative and quantitative differences of the melanosomal matrix proteins between the ellipsoidal-lamellar melanosomes of B16 melanoma and the spherical-granular melanosomes of Harding Passey (HP) melanoma by electron microscopy and SDS (sodium dodecyl sulfate)-PAGE (polyacrylamide gel electrophoresis). The purity of the melanosomes at each step of the sample preparations was assayed by per cent distribution of cytoplasmic marker enzymes and proteins. Characterization of the melanosomal matrix was carried out in material purified by the two steps of sucrose density gradient ultracentrifugation and membrane dissociation with BRIJ-35. Eighty-three percent of the matrix proteins were solubilized from both B16 and HP by guanidine HCl (GH), which also caused marked ultrastructural changes in different ways. The inner matrix of HP completely disintegrated into fine grains whereas the matrix of B16 showed a great loss in electron density and was degraded, though its basic framework remained unchanged. Under SDS-PAGE, the melanosomal matrix was dissociated into 14 polypeptide bands with respect to size and charge density, 10 of which (63-85% of total proteins solubilized by GH) were common to both B16 and HP. A significant quantitative difference was noted in the relative amounts of these common proteins. The remaining four were unique in mol wt to each form of melanosome though their relative amounts were low. It is suggested that these chemical differences, ie, quantitative and qualitative, of the matrix proteins are responsible for the ultrastructural differentiation of melanosomes. (Author abstract) (21 Refs)

34. HETEROGENEITY IN SURFACE ANTIGEN AND GLYCOPROTEIN EXPRESSION OF CELL LINES DERIVED FROM DIFFERENT MELANOMA METASTASES OF THE SAME PATIENT. IMPLICATIONS FOR THE STUDY OF TUMOR ANTIGENS.

Albino AP, Lloyd KO, Houghton AN, Oettgen HF, Old LJ
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Exp Med; 154(6):1764-1778 1981

Three melanoma cell lines (DX-1,-2, and-3) derived from separate metastatic foci of patient DX (a 70 yr old woman) were examined for phenotypic differences in growth, morphology, and expression of cell surface antigens and glycoproteins. DX-1 and-2 accumulated visible pigment; DX-3 cell appeared unpigmented. DX-2 and-3 cell lines grew as attached monolayers, while DX-1 showed a marked tendency to grow in suspension after initial attachment as microcolonies of rounded cells. Only DX-1 and-3 cells expressed D-locus human WBC antigen surface antigens. Less marked but characteristic differences were detected in the expression of other cell surface antigens. DX-2 and-3 exhibited similar profiles of cell surface glycoproteins in the high mol wt region, with 90,000 and 120,000 mol wt components being particularly prominent. DX-2 had an additional prominent component of 60,000 mol wt which was only weakly labeled in DX-3. DX-3 exhibited two major glycoproteins in the low mol wt region of 32,000 and 27,000. Only one major glycoprotein of 90,000 mol wt was labeled in DX-1 monolayer cells. Sera from patient DX reacted only with surface antigen of autologous DX-2; the highest reactivity was in the IgG fraction. The time-course of DX autologous reactivity was examined. Absorption analysis indicated that the DX-2 antigen was a class 1 melanoma antigen; the antigen was also detectable in much lower but demonstrable amounts in DX-1 and-3 cells. No other cell type tested exhibited the class 1 DX melanoma antigen. (21 Refs)

35. MONOCLONAL ANTIBODIES AGAINST RECEPTOR FOR EPIDERMAL GROWTH FACTOR INDUCE EARLY AND DELAYED EFFECTS OF EPIDERMAL GROWTH FACTOR.

Schreiber AB, Lax I, Yarden Y, Eshhar Z, Schlessinger J
Dept. Chemical Immunology, Weizmann Inst. Science, 76100 Rehovot, Israel
Proc Natl Acad Sci USA; 78(12):7535-7539 1981

Mice were immunized with human epidermoid carcinoma cells (A-431 cell line) that possess an unusually high number of membrane receptors for epidermal growth factor (EGF). Spleen cells from these mice were fused with NSI cells, a non-secreting murine myeloma. The immunoglobulins secreted by the obtained hybridomas were screened for specific binding to A-431 cells and selected according to their ability to inhibit the binding of radiolabeled EGF to the membrane of A-431 cells. Several antibodies secreted by cloned hybrid lines were found to inhibit the binding of radiolabeled EGF to membrane receptors of living A-431 cells, human foreskin fibroblasts, and mouse 3T3 fibroblasts and also to membrane preparations from A-431 cells. These monoclonal antibodies induced the early and delayed biological effects mediated by EGF. Like EGF, the antibodies induced morphological changes in A-431 cells and enhanced the phosphorylation of endogenous membrane proteins in membranes from these cells. They also stimulated DNA synthesis in human foreskin fibroblasts. These observations support the notion that the biological information of the EGF-receptor complex resides in the membrane receptor. Furthermore, the antibodies offer a powerful tool to study the structure, processing, and mode of action of EGF receptors. (Author abstract) (34 Refs)

36. LACTOPEROXIDASE-CATALYZED IODINATION OF MEMBRANE PROTEINS IN NORMAL AND NEOPLASTIC EPIDERMAL CELLS.

Brysk MM, Snider JM

Dept. Dermatology, Univ. Texas Medical Branch, Galveston, TX, 77550

J Invest Dermatol; 78(1):24-27 1982

Cell surface proteins of normal human, mouse, and rat cells in primary culture, of human basal cell carcinoma, and of carcinogen-transformed cell lines were examined by lactoperoxidase-catalyzed iodination. Autoradiography was used to record the distribution of label in the polypeptide subunits separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. There was no significant difference in the results for normal cells of human, mouse, and rat. On the other hand, carcinogen-transformed mouse cells had many more labeled polypeptide bands of widely distributed mol wt. The iodination profiles from human basal cell carcinoma cells were much more akin to those from normal cells than to those from carcinogen-transformed cells. Treatment of iodinated cells with proteolytic enzymes visibly altered the polypeptide bands. (Author abstract) (21 Refs)

REVIEWS

37. KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN.

Myskowski PL, Romano JF, Safai B

(c/o Safai) 425 E. 67th St., New York, NY, 10021

Cutis; 29(1):31-34 1982

The incidence, clinical features, associated conditions, pathogenesis, and prognosis of a new form of Kaposi's sarcoma (KS) are discussed. Within the last three yr 54 such cases showed differences from traditional KS including a mean age of 39 yr, all men with bisexual or homosexual preference, and geographic clustering in New York City and California. Clinical features of the new variant of KS include early presence of lymph node and/or mucous membrane involvement, pityriasis rosea-like pattern of skin lesions primarily on the head, trunk, and upper extremities, and systemic complaints. Associated conditions include pneumocystis carinii pneumonia, herpes simplex infection, toxoplasmosis, and cryptococcosis, but not secondary neoplasms. A history of prior sexually transmitted disease in new KS patients suggests a relationship to KS development. Cytomegalovirus infection was reported in 94% of cases. Immune defects are also suspected in young homosexual KS patients. The prognosis for the new form of KS is less favorable, with a 20% mortality rate at the present time. Effects of therapy are difficult to evaluate thus far. Awareness of the features of the new KS will enable practitioners to better recognize this disease. (18 Refs)

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ICRDB CANCERGRAM

MELANOMA AND OTHER SKIN CANCER

Diagnosis, Treatment

SERIES CT22 No. 82/07

JULY, 1982

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DIAGNOSIS

1. DETERMINATION OF URINARY MELANOGEN IN 40 CASES OF MALIGNANT MELANOMA.

Bucciarelli M, Bertazzoni MG, Motolese A
Clinica Dermosifilopatica, Universita di Modena, Modena, Italy
Chron Dermatol; 12(3):375-379 1981

Urinary melanogen was determined in 40 patients with malignant melanoma (MM) and in 12 controls (patients with other diseases), using Thormahlen's test. The results of the test were always negative (amber color) in the controls. Of the 20 MM patients without clinical evidence of metastases, the results of the test were negative in 17 and slightly positive in 3 (pale

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green color). Of the six MM patients with lymph nodes or skin metastases surrounding the lesion, the results of the test were negative in one and slightly positive in five. Of the 14 MM patients with visceral metastases, the results of the test were negative in 1 case, positive in 7 (intense green color) and strongly positive in 6 (blue-green color). When the test was repeated later on in 14 cases, the results remained unchanged in 10 patients who did not show clinical change; however, in 4 patients who previously had negative or slightly positive results, the color changed, indicating more positive results following the appearance of metastases. The test was useful in prognosis of MM. (15 Refs) (In ITA)

2. NEURONE SPECIFIC ENOLASE: AN AID TO THE DIAGNOSIS OF MELANOMA AND NEUROBLASTOMA.

Dhillon AP, Rode J, Leathem A

Bland-Sutton Inst. Pathology, The Middlesex Hosp., London WIP 7PN, England

Histopathology; 6(1):81-92 1982

Staining for neurone specifice enolase (NSE) was investigated as a possible means of establishing the histogenic origin of tumors derived from amine precursor uptake and decarboxylation (APUD) cells, specifically melanoma and neuroblastoma. APUD tissues and tumors that were examined included pituitary, thyroid, parathyroid, adrenal medulla, pancreas, carcinoid, medullary carcinoma of the thyroid, parathyroid adenoma, and pancreatic islet cell hyperplasia. Cytoplasmic staining for NSE was observed in the APUD elements and tumors derived from them. Clear fibrillary and cytoplasmic staining for NSE was demonstrated in 2/3 cases of neuroblastoma, but staining was slight in the other case. The appearance of fibrillary and cytoplasmic staining was distinct from the pattern presented by melanoma. Fifteen of the 16 melanomas studied stained positively for NSE; non-neoplastic melanocyte staining varied from none to moderate. Lymphoma and Ewing's sarcoma showed no staining. Of 23 pulmonary tumors, one poorly-differentiated squamous cell, one small cell anaplastic, and two large cell anaplastic carcinomas showed slight cytoplasmic staining for NSE. In the absence of the usual positive diagnostic criteria, demonstration of NSE may contribute to the diagnosis of melanoma or neuroblastoma. (18 Refs)

3. URINARY FREE AND CONJUGATED 5-S-CYSTEINYLDOPA IN NORMAL SUBJECTS AND IN PATIENTS WITH MELANOMA.

Graef V, Paul E

Inst. Clinical Chemistry and Pathobiochemistry, Univ. Giessen, Giessen, W. Germany

Br J Dermatol; 106(1):53-57 1982

We measured free and total 5-S-cysteinyldopa excretion in 24-hr urine specimens from 9 patients with malignant melanoma and 45 controls, and found that the levels of 5-S-cysteinyldopa excretion (measured by a fluorometric method) were greatly increased in the melanoma patients. The conjugates were hydrolyzed by enzymatic treatment with beta-glucuronidase/arylsulfatase, and we found that the percentage of conjugated 5-S-cysteinyldopa was higher in urines with a low content of free 5-S-cysteinyldopa than in those with a higher concentration. (Author abstract) (8 Refs)

4. AN ULTRASTRUCTURAL STUDY OF THE MONONUCLEAR CELL INFILTRATE OF MYCOSIS FUNGOIDES AND POIKILODERMA ATROPHICANS VASCULARE.

Chu AC, Morgan EW, MacDonald DM

(c/o MacDonald) Dept. Dermatology, Guy's Hosp., St. Thomas' St., London SE1 9RT, England

Clin Exp Dermatol; 7(1):11-19 1982

Skin biopsies from patients with pre-mycotic eruptions and plaque and tumid mycosis fungoides (MF) were examined by electron microscopy to assess the value of the presence of abnormal lymphoid cells in early diagnosis of MF. In 21/25 specimens from patients with untreated MF and in all 3 from patients with poikiloderma atrophicans vasculare, mononuclear cells infiltrated the epidermis. In all dermal filtrates examined, abnormal lymphoid cells were conspicuous; the cells possessed irregular nuclear outlines ranging from mild indentation to grossly cerebriform shapes. In the dermis, lymphoid cells comprising 30-60% of the infiltrate were seen in a mixed cellular infiltrate composed of normal mature lymphocytes, histiocytes, mast cells, eosinophils, and occasional polymorphonuclear WBC and plasma cells. Lymphoblasts were identified in dermal infiltrates of two patients with tumid MF. Bizarre histiocytic cells resembling the interdigitating reticulum cell of lymph node T cell areas were observed. In epidermal infiltrate, abnormal lymphoid cells infiltrates singly between keratinocytes and less frequently in groups, forming Pautrier microabscesses. Langerhans cells were observed only in the epidermis, usually isolated but occasionally in contact with lymphoid cells. The diagnostic importance of ultrastructural findings in MF is affirmed. (27 Refs)

5. CUTANEOUS T-CELL LYMPHOMA, MULTILOBATED TYPE.

van der Putte SC, Toonstra J, De Weger RA, Van Unnik JA

Inst. Pathology, Pasteurstraat 2, 3511 HX Utrecht, The Netherlands

Histopathology; 6(1):35-54 1982

Problems related to the distinction and accurate classification of malignant and pseudomalignant lymphoreticular proliferation are demonstrated by three cases. Specimens from three lesions were examined using light microscopy, electron microscopy, cytochemistry, immunohistology, and immunofluorescence. All three cases occurred in elderly men (53, 55, and 53 yr old) with tumorous lesions restricted to one region of the skin and remaining so for a considerable time with a relatively benign course. Histopathologically, in one case the cutaneous infiltrates showed sparing of epidermis and upper dermal zone and demonstrated the peculiar combination of pronounced nuclear lobation and marginal nucleoli. The two other cases were similar but had an even more benign course; histopathologically, a less monotonous infiltrate of cells with less marked nuclear lobation was evident. Cases similar to those reported may have been misinterpreted as lymphoid hyperplasia, malignant B-cell lymphoma, or reticulum cell sarcoma of the skin. The three cases were classified as cutaneous T-cell lymphoma, multilobated type. (57 Refs)

6. THE NEUROENDOCRINE MERKEL CELL CARCINOMA OF THE SKIN.

Gloor F, Heitz U, Hofmann E, Hoefler H, Maurer R
Pathologisches Institut, Kantonsspital, CH-9007 St. Gallen, Switzerland
Schweiz Med Wochenschr; 112(5):141-148 1982

Seven primary skin tumors from five women and two men were analyzed by light and electron microscopy and immunocytochemistry. The tumors were localized on the face (3 tumors) and on the extremities. The max diameter was between 1 and 3.5 cm. Two tumors metastasized to the regional lymph nodes 4 mo after excision of the primary, one tumor metastasized to the regional lymph nodes after 5 yr and the patient died of multiple metastases 8 yr after excision of the primary on the forearm. No local recurrences developed. The tumors occurred in the dermis with frequent infiltration of the sc tissue. The epidermis was intact. The tumor cells formed large solid clusters, while their cytoplasm was faintly basophilic and formed a small rim round the large pale nucleus. In electron microscopy many cells displayed cytoplasmic electron-dense secretory granules with a mean diameter of approx 100 nm. Immunocytochemistry showed that a large number of cells in all tumors contained neuron specific enolase and many cells of four tumors yielded formaldehyde-induced fluorescence. The tumors are therefore of neuroendocrine origin and may derive from Merkel cells. They frequently give rise to erroneous diagnosis of metastasis of carcinoma or malignant lymphoma to the skin. (Author abstract) (29 Refs) (In GER)

7. AN ULTRASTRUCTURAL AND IMMUNOHISTOCHEMICAL STUDY ON MANDIBULAR LESION OF LETTERER-SIWE DISEASE.

Ide F, Sano R, Shimura H, Kusama K, Umemura S
Dept. Pathology, Nihon Univ. Sch. Dentistry, 1-8-13, Surugadai Kanda, Chiyoda-ku, Tokyo 101, Japan
J Oral Pathol; 10(6):386-397 1981

Ultrastructural and immunohistochemical features of Letterer-Siwe disease from the mandible of a 1-yr-old boy are reported. Two types of cells were revealed: Langerhans cell granule-containing cells and ordinary histiocytes. The former were related to the cytoplasmic membrane. The variable number of granules was probably due to differences in cell maturation and functional activity of clear cells. The ordinary histiocytes stained darkly and had numerous lysosomes and phagosomes and did not contain Langerhans cell granules. Most proliferating cells with indented nuclei and multinucleated giant cells were negative for lysozyme, while polymorphonuclear WBC were strongly positive. IgG was detected in some proliferating cells without peculiar nuclei, but cytoplasmic IgM, IgA, IgD, and IgE were not detected. Most cells with indented nuclei were negative for immunoglobulins. These findings and those in the literature suggest that histiocytosis X might be a reactive or tumorous condition in which the Langerhans cell is the stem cell. The ordinary histiocytes may be the ultrastructural counterpart of the lysosome-rich cells without Langerhans cell granules and the Langerhans cell granule-containing cells may be the counterpart of the acid phosphatase-, esterase, and lysozyme- negative cells which may be important in the pathogenesis of histiocytosis X. (40 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

8. DNCB SKIN TEST IN CASES OF MALIGNANT MELANOMA.

Ehring F, Loth H
Special Clinic Hornheide, Dorbaum 48, D-4400 Munster-Handorf, W. Germany
J Cancer Res Clin Oncol; 102(2):185-187 1981

Two hundred sixty-nine patients suffering from malignant melanoma were sensitized with DNCB acetone soln. The intensity of the skin reaction was normally independent of both the current stage and the further progression of the disease. (Author abstract) (9 Refs)

9. BLOOD LYMPHOCYTE SUBPOPULATIONS IN MYCOSIS FUNGOIDES AND THEIR FUNCTIONS IN VITRO.

Gu SQ, Petrini B, Von Stedingk LV, Thyresson N, Wasserman J
Dept. Dermatology, Karolinska Sjukhuset, S-104 01 Stockholm 60, Sweden
Acta Derm Venereol (Stockh); 61(6):487-490 1981

T-lymphocyte subpopulations, PWM stimulated in vitro Ig production by mononuclear cells, and spontaneous cell-mediated cytotoxicity (SCMC) were determined in patients with Mycosis fungoides (MF) as well as in sex- and age-matched normal controls. We were able to confirm our earlier findings of a significantly higher frequency of T-lymphocytes with Fc-receptors for IgG (Tg cells) and a proportion of T lymphocytes with Fe receptors for IgM (Tm cells) not significantly differing from normal controls. As defined by monoclonal antibodies, the proportion of T-helper cells (Leu3A) was significantly lower, whereas the T-suppressor cells (Leu2A) were in the range of normal controls. The PWM stimulated and spontaneous Ig synthesis in vitro was lower in MF patients whereas there was no difference in the SCMC activity, in comparison with normal controls. The lower frequency of T-helper cells in the peripheral blood may be explained by their migration to the skin. (Author abstract) (14 Refs)

10. T LYMPHOCYTES WITH FC-IGG RECEPTORS IN SKIN CANCERS.

Vena GA, Angelini G, D'Ovidio R, Lospalluti M, Meneghini CL
Dept. Dermatology, Univ. Bari, Bari, Italy
Acta Derm Venereol (Stockh); 61(6):555-558 1981

The proportion of peripheral blood lymphocytes with receptors for the Fc fragment of IgG (Tg) has been investigated in 25 patients with squamous cell carcinoma of the skin, in 25 patients with basal cell carcinoma of the skin, and in 33 controls. In patients with squamous cell carcinoma the results showed elevated values for Tg lymphocytes and a negative correlation between these T cells and the lymphocyte response to PHA and ConA. In patients with basal cell carcinoma the values for Tg lymphocytes were normal. (Author abstract) (12 Refs)

CHEMOTHERAPY

11. CLINICAL TRIAL OF CHLOROZOTOCIN, DTIC, AND DACTINOMYCIN IN METASTATIC MALIGNANT MELANOMA.

Samson MK, Baker LH, Cummings G, Talley RW, McDonald B, Bhathena DB
Dept. Oncology, Univ. Health Center, 4201 St. Antoine 7-C, Detroit, MI, 48201
Cancer Treat Rep; 66(2):371-373 1982

Thirty evaluable patients with metastatic malignant melanoma were treated with a combination of chlorozotocin, dacarbazine (DTIC), and dactinomycin. One complete and four partial responses were achieved, for an overall response rate of 17%. Cumulative myelotoxicity was noted, as well as universal gastrointestinal intolerance. One patient developed probable drug-related nephrotoxicity. A survival advantage was noted for responding patients. We conclude that the addition of chlorozotocin did not improve response rate or response duration and that further trials with this drug combination cannot be recommended. (Author abstract) (8 Refs)

12. ANGIOGRAPHIC APPEARANCE OF RECURRENT MALIGNANT MELANOMA BEFORE AND AFTER INTRA-ARTERIAL CHEMOTHERAPY.

Charnsangavej C, Chuang VP, Wallace S, Soo CS, Bowers T
Dept. Diagnostic Radiology, M.D. Anderson Hosp. and Tumor Inst. Univ. Texas System Cancer Center, 6723 Bertner Ave., Houston, TX, 77030
Radiology; 142(2):347-349 1982

Intra-arterial infusion of chemotherapeutic agents (CDDP alone or combined with DTIC) was used to treat recurrent melanoma in 22 patients. In 17 cases, sequential arteriograms were obtained before and after infusion to monitor the procedure. Pre-treatment angiograms usually demonstrated rounded nodules with a homogeneous, hypervascular stain. In three patients, additional deep-seated lesions which were not palpable clinically were detected by angiography. Arteriograms of those patients who responded to chemotherapy revealed partial or complete disappearance of tumor stain. A 46% response rate was observed. The authors feel that angiography is valuable in pretreatment diagnosis and post-treatment evaluation of recurrent melanoma. (Author abstract) (8 Refs)

RADIOTHERAPY

13. THE POTENTIAL FOR ADJUVANT RADIOTHERAPY IN CHOROIDAL MELANOMA.

Char DH, Phillips TL
Ocular Oncology Unit, Univ. California, Science 315, San Francisco, CA, 94143
Arch Ophthalmol; 100(2):247-248 1982

Controversy exists regarding the efficacy of enucleation in the management of choroidal melanoma. The effect of any form of ocular therapy on the prevalence of choroidal melanoma metastases is unknown. In a number of other systemic tumors, preoperative irradiation may lessen the occurrence of widespread disease. This type of therapeutic approach might be useful in the management of high-risk choroidal melanoma. In preliminary studies using 2,000 rad of preenucleation irradiation in patients with choroidal melanoma who have a poor prognosis, we have not observed notable morbidity. There are a number of limitations to the use of this adjunct therapy in choroidal melanoma management; however, a prospective national randomized trial of preenucleation irradiation in patients with high-risk choroidal melanoma might allow us to indirectly determine the effect of enucleation on the prevalence of choroidal melanoma metastases as well as delineate the potential role of this type of adjunct therapy in ocular melanoma. (Author abstract) (23 Refs)

SURGERY

14. NARROWER MARGINS FOR CLINICAL STAGE I MALIGNANT MELANOMA.

Day CL, Mihm MC, Sober AJ, Fitzpatrick TB, Malt RA
(c/o Malt) Surgical Services, Massachusetts General Hosp., Boston, MA, 02114
N Engl J Med; 306(8):479-482 1982

Surgery for cutaneous malignant melanomas (MM), recognition, and curability are reviewed. Misconceptions about the curability of MM exist because the current high survival rates (SR) are not widely known. Present good SR result from earlier diagnosis. Thickness of the primary melanoma is the dominant prognostic factor for clinical Stage I disease, and the relation between thickness and survival is a step function in which the risk of death increases sharply at thickness values of 0.85, 1.70, and 3.65 mm. SR are approx the same whether histologic evidence of regression is present or absent and whether regional lymph nodes are electively removed or left intact. Conflicting reports on the effects of surgical margins on chances of survival and of local recurrence have resulted when thickness of the primary melanoma has not been considered. Studies using primary tumor thickness as a correlate of survival have shown that the magnitude of surgical margins has no effect on length of survival and imply that an arbitrary radius of 5 cm is almost certainly an error. For patients with clinical Stage I disease, excisions of no more than 1.5 cm of clinically normal skin bordering MM that rarely metastasize are recommended. All other MM should be excised with a 3.0-cm radius measured from the edge of MM. Recommendations apply only to MM specifically cited. (30 Refs)

CASE REPORTS

15. PRIMARY BILATERAL MALIGNANT MELANOMA OF THE CHOROID. CASE REPORT WITH A CONTRIBUTION TO HISTOGENESIS OF THIS TYPE OF TUMOR.

Lau T
Pathologisches Institut des Krankenhauszweckverbandes, Franziskanergasse 5, D-8900 Augsburg, W. Germany
Klin Monatsbl Augenheilkd; 179(5):333-335 1981

A 54-yr-ld woman underwent enucleation of the left eye for treatment of primary bilateral melanoma of the choroid. Histologic examination of the surgical specimen revealed the presence of a thin layer of spindle cells between the tumor and the sclera. The patients died 2 mo after surgery due to a pulmonary embolism. Autopsy of the right eye led to a final diagnosis of spindle cell melanoma (Type B) of the choroid. It was concluded that the malignancy originated in the thin layer of spindle cells found on histologic examination. (17 Refs) (In GER)

16. LEIOMYOSARCOMA OF THE SKIN: A CASE REPORT.

Aranha GV, Molnar ZV, Reyes CV, Skladzien G, Valadka VT
Hines Veterans Admin., P.O. Box 1044, Hines, IL, 60141
J Surg Oncol; 19(2):87-89 1982

A middle-aged man presented with an ulcerated nodule of the right posterior thigh that was histologically evaluated as leiomyosarcoma of the skin. A wide excision of the tumor was followed by split-thickness skin grafting. Leiomyosarcomas of the skin and subcutaneous tissue are rare tumors, usually occurring in the proximal lower extremities. The treatment of choice is a wide local excision with a 3-to 5-cm margin including the subcutaneous tissue and fascia. The defect is covered by a split-thickness skin graft. (Author abstract) (8 Refs)

17. BASAL CELL CARCINOMA OF THE SCROTUM: A CASE REPORT AND LITERATURE REVIEW.

Greider HD, Vernon SE
Dept. Pathology, St. Francis Hosp., Miami Beach, FL
J Urol; 127(1):145-146 1982

Basal cell carcinoma of the scrotum is a rarely occurring lesion that must be differentiated from the more common squamous cell carcinoma, as well as chronic dermatitis or chronic fungal infection. We report a case of basal cell carcinoma of the scrotum and review the literature. This case serves as a reminder that these lesions do occur on the scrotal skin and that, unlike squamous cell carcinomas, they are curable with simple wide excision. (Author abstract) (10 Refs)

18. MYCOSIS FUNGOIDES D'EMBLEE: A RARE PRESENTATION OF CUTANEOUS T-CELL LYMPHOMA.

Blasik LG, Newkirk RE, Dimond RL, Clendenning WE
(c/o Clendenning) Section Dermatology, Hitchcock Clinic, Maynard St., Hanover, NH, 03755
Cancer; 49(4):742-747 1982

A case of the d'emblee variant of mycosis fungoides is presented to confirm the validity of this rare variant of cutaneous T-cell lymphoma. The patient had rapidly progressing cutaneous tumors of mycosis fungoides with no internal organ or nodal involvement at the onset of the disease. This was confirmed at a laparotomy, which was done to remove a uterine leiomyoma. The classic light microscopy was confirmed by electron microscopy. Postmortem findings showed a remarkable degree of 'epitheliotropism.' The d'emblee form of mycosis fungoides has been disputed by some who argue that these cases represent a lymphoma that begins elsewhere and has secondary skin involvement. In this patient there was an opportunity, within a few wk of the onset of the problem, to do an extensive staging workup, including laparotomy. No evidence of internal lymphoma was found. (Author abstract) (15 Refs)

19. THE GIANT KERATOACANTHOMA OF THE PALPEBRAL REGION. (DIAGNOSTIC AND THERAPEUTIC PROBLEMS).

Flament J, Kouhil M, Amiar M-K, Boukoffa O-S, Forest M
Service d'Ophthalmologie, C.H.U.-Strasbourg, Strasbourg, France
Bull Soc Ophtalmol Fr; 81(8/9):611-615 1981

Two unusual cases of palpebral keratoacanthoma (KA) are reported. A 75-yr-old woman presented with a large cutaneous tumor in the region of the left external canthus. In the second case, a 73-yr-old man presented with a giant KA of the left inferior eyelid. In both cases, surgical excision of the tumor followed by a skin graft as the treatment. Although a definitive diagnosis of KA was established in both cases, there was no history of any spontaneous regression which is generally found in cases of palpable KA. (17 Refs) (In FRE)

20. SMALL-CELL NEUROEPITHELIAL TUMOR OF SKIN: A MERKEL-CELL NEOPLASM?

Pollack SV, Goslen JB
Duke Univ. Medical Center, P.O. Box 3915, Durham, NC, 27710
J Dermatol Surg Oncol; 8(2):116-122 1982

Two cases of small-cell undifferentiated neuroepithelial skin tumors are discussed. The first patient, a 63-yr-old man, presented with a small lesion on the scalp which persisted after cryotherapy. A tumor-free plane was reached after three stages of excision; the patient has remained tumor free for 4 mo. Histologic examination of the tumor revealed tightly packed cells and infiltration of tumor between collagen bundles. Individual cells had basophilic nuclei with nuclear molding and scant cytoplasm. Electron microscopy revealed membrane-limited, dense core granules primarily in the cytoplasm. The second patient, a 68-yr-old man, presented with a nodule on the upper left chest wall. Excision and left axillary node dissection were performed. Satellite tumors developed 2 mo postoperatively. Chemotherapy followed by radiotherapy produced no decrease in tumor mass. Postmortem examination revealed metastases in the liver, lymph nodes, vertebral bone marrow, and bilateral pleura. Histological examination revealed uniform neoplastic cells with small round hyperchromatic nuclei with scant cytoplasm both in skin and metastatic tumors. Small-cell neuroepithelial tumor should be suspected when an undifferentiated carcinoma with dense core granules confined to the dermis or subcutaneous tissue is seen. Therapy should consist of wide local excision and/or Mohs' surgery combined with node dissection when clinical disease is suspected. (26 Refs)

21. AGGRESSIVE KERATOACANTHOMA AND INTERNAL MALIGNANT NEOPLASM.

Fathizadeh A, Medenica MM, Soltani K, Lorincz A, Griem ML
Section Dermatology, Univ. Chicago, 950 E 59th St., Box 409, Chicago, IL, 60637
Arch Dermatol; 118(2):112-114 1982

A patient with an abdominal mass, ascites, and a pleural effusion had an aggressive keratoacanthoma on her lower lip. Malignant cells, presumably originating from an ovarian carcinoma, were found in pleural and ascitic fluids. This case and previously reported cases indicate that multiple or aggressive keratoacanthomas may be seen in association with internal malignant neoplasms or compromised immunologic responsiveness. (Author abstract) (13 Refs)

22. REGRESSING ATYPICAL HISTIOCYTOSIS: A CUTANEOUS PROLIFERATION OF ATYPICAL NEOPLASTIC HISTIOCYTES WITH UNEXPECTEDLY INDOLENT BIOLOGIC BEHAVIOR.

Flynn KJ, Dehner LP, Gajl-Peczalska KJ, Dahl MV, Ramsay N, Wang N
Dept. Dermatology, Univ. Hosp., Box 98, 420 Delaware St., SE, Minneapolis, MN, 55455
Cancer; 49(5):959-970 1982

Regressing atypical histiocytosis (RAH) of skin is a cutaneous noduloulcerative proliferation of atypical neoplastic histiocytes with concomitant polymorphous inflammation, frequently pronounced epidermal hyperplasia, and an unexpectedly indolent biologic course. Spontaneous regression and recurrence without systemic spread were the course in follow-up periods of over 6 yr. Histopathologically, characteristic-appearing atypical mononuclear and multinucleated 'RAH' cells showed erythrophagocytosis as well as ultrastructural, surface marker, and enzyme cytochemical features indicating histiocytic differentiation. Cytogenetic analysis showed aneuploidy and several marker chromosomes including 14q+. Its benign biologic course clearly distinguished this entity from malignant histiocytosis, large cell lymphoma, and Hodgkin's disease. The histiocytic atypical cells further distinguished it from the T-cell lesions of the skin, such as mycosis fungoides and lymphomatoid papulosis. This entity is readily confused with malignant lymphoreticular disease, melanoma, or squamous carcinoma. (Author abstract) (68 Refs)

23. NEUROTROPIC MELANOMA OF THE VULVA.

Warner TF, Hafez GR, Buchler DA
Dept. Surgical Pathology, Clinical Sciences Center, Univ. Wisconsin, Madison, WI, 53792
Cancer; 49(5):999-1004 1982

A spindle cell melanoma of the clitoris was associated with a large area of lentiginous melanocytic dysplasia in the vulva of a 51-yr-old woman. There was extensive neoplastic infiltration of the dermis, a desmoplastic reaction, and replacement of perineurial and Schwann cells by tumor cells (neurotropism). The superficial dysplastic components were pigmented, but melanosomes were not identified in a lymph node metastasis. Here the internuclear areas strongly resembled neuropil. Vulvar melanoma is rare, and this is the first report of neurotropic melanoma in this site. (Author abstract) (21 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

24. THE RELATIONSHIP OF MALIGNANT MELANOMA, BASAL AND SQUAMOUS SKIN CANCERS TO INDOOR AND OUTDOOR WORK.

Beral V, Robinson N
Epidemiological Monitoring Unit, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Br J Cancer; 44(6):886-891 1981

An analysis of occupational incidence data for malignant melanomas and squamous- and basal-cell carcinomas of the skin in England and Wales from 1970 to 1975 is reported. The occupational pattern for melanomas of the trunk and limbs differed markedly from the pattern for melanomas of the head, face and neck. Office work was associated with a large excess of melanomas of the trunk and limbs. In contrast, outdoor work was associated with an excess of melanomas of the head, face and neck and was also associated with an excess of squamous- and basal-cell carcinomas of the skin. This suggests that prolonged occupational exposure to sunlight is an important cause of squamous- and basal-cell carcinomas and of melanomas of the head, face and neck, but not of melanomas on other parts of the body. The high rate of lesions on the trunk and limbs in office workers may reflect their sunbathing or other recreational habits: but it contrasts clearly with other indoor work, where there is generally low rate of all forms of skin cancer. (Author abstract) (20 Refs)

SELECTED PRECLINICAL STUDIES

25. REGRESSION OF MALIGNANT MELANOMA IN A DOG BY LOCAL INJECTIONS OF A PARTIALLY PURIFIED PREPARATION CONTAINING HUMAN ALPHA-LYMPHOTOXIN.

Khan A, Martin ES, Webb K, Weldon D, Hill NO, Duvall J, Hill JM
Dept. Immunotherapy, Wadley Inst. Molecular Medicine, 9000 Harry Hines, Dallas, TX
Proc Soc Exp Biol Med; 169(2):291-294 1982

A 12-yr-old male dog with a rapidly growing melanoma of the mouth received injections of partially purified human lymphotoxin intratumorally at 2-to 5-day intervals. The dose of lymphotoxin activity ranged from 600-2,100 units/injection; a total of 13,320 units was injected over a 30-day period. Tumor size decreased 30% during the first 3 days, accompanied by sloughing of the tumor; regression continued, and the mass disappeared completely by day 20. No untoward effects of treatment were observed in the dog. Biopsy from the tumor site 12 days after completion of treatment showed fibrosis and lymphocytic infiltration but no tumor cells. Six months later, however, sc metastatic malignant melanoma was found in the neck. Alpha-lymphotoxin-containing human preparations may be suitable for human trials. (13 Refs)

26. SMALL CONGENITAL NEVOCELLULAR NEVI AND THE RISK OF CUTANEOUS MELANOMA.

Rhodes AR, Melski JW
Div. Dermatology, Hunnewell-3, Children's Hosp. Medical Center, 300 Longwood Ave., Boston, MA, 02115
J Pediatr; 100(2):219-224 1982

The relative risk of melanoma associated with small congenital nevi was estimated by comparing the published frequency of histologically documented nevocellular nevi in newborn infants with the frequency of; (1) congenital nevi at the tumor site, ascertained by history in 134 patients with melanoma; and (2) tumor-associated nevi with congenital features in 234 melanoma specimens. A 21-fold increase in melanoma risk was estimated for persons with small congenital nevi when nevi were ascertained by history, and a 3-to 10-fold increase in risk when nevi were ascertained by histology. Based on these approximations of relative risk from historic and histologic methods of detection, persons with small congenital nevi who live to age 60 are estimated to have cumulative risks for melanoma of 4.9/100 and 0.8 to 2.6/100, respectively. The increased risk is related presumably to the markedly increased probability of melanoma arising in association with small congenital nevi. In other words, small congenital nevi may represent precursors for at least some cases of cutaneous melanoma. The estimated risks are highly dependent on the specificity of methods used for ascertainment of congenital nevi. (Author abstract) (32 Refs)

27. SOMATIC CELL HYBRIDS PRODUCING INHIBITORS OF MELANOTIC MELANOMA TYROSINE HYDROXYLASE.

Hakim AA
180 Longwood Drive, Kankakee, IL, 60901
Experientia; 38(2):267-270 1982

Splenic lymphocytes from BALB/c mice pre-immunized with purified tyrosine hydroxylase (TH) were fused with murine myeloma N/1 cells. Supernatants of only two from the large number of cloned cell hybrids contained an inhibitor of TH. (Author abstract) (29 Refs)

28. AROTINOIDS: A NEW CLASS OF RETINOIDS WITH ACTIVITIES IN ONCOLOGY AND DERMATOLOGY.

Bollag W
Pharma Res. Dept., F. Hoffmann-La Roche and Co. Ltd., CH-4002 Basle, Switzerland
Cancer Chemother Pharmacol; 7(1):27-29 1981

The arotinoid p-[(E)-2-(5,6,7,8-tetramethyl-2-naphthyl)propenyl] benzoic acid ethyl ester (Ro 13-6298) was tested for therapeutic effect against experimental skin papillomas (PL) and carcinomas (CC) in mice. PL and CC were induced by painting the skin with 7,12-dimethylbenz(a)anthracene and croton oil. Mice received Ro 13-6298 dissolved in arachis oil ip or po 1x or 5x/wk for 2 wk. A therapeutic index was calculated as the ratio of the lowest daily ip dose given for 2 wk causing a defined degree of hypervitaminosis A (HVA) and the lowest dose given 1x/wk for 2 wk producing a regression of PL of approx 50%. Ro 13-6298 given ip produced regression of PL at a dose rate of 0.2 mg/kg 1x/wk and 49.1% regression at a dose rate of 0.05 mg/kg. Ro 13-6298 given orally produced 43.9% regression at a dose rate of 0.02 mg/kg 5x/wk. ED50 for Ro 13-6298 was 0.05 mg/kg compared with 25 mg/kg for the aromatic retinoid etretinate Ro 10-9359 and 400 mg/kg for all-trans-retinoic acid, both reported previously. Ro 13-6298 produced 74.9% regression of CC at a dose 0.2 mg/kg 5x/wk and 84.1% regression of CC at a dose rate of 0.3 mg/kg 5x/wk; at both dose rates some HVA was produced. Results indicate Ro 13-6298 as a candidate for clinical trials in clinical dermatology and oncology. (5 Refs)

29. TRANSFORMING GROWTH FACTOR(S) PRODUCTION ENABLES CELLS TO GROW IN THE ABSENCE OF SERUM: AN AUTOCRINE SYSTEM.

Kaplan PL, Anderson M, Ozanne B
Dept. Microbiology, Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, TX, 75235
Proc Natl Acad Sci USA; 79(2):485-489 1982

Kirsten murine sarcoma virus (KiMSV)-transformed rat-1, normal rat kidney (NRK), and BALB/c 3T3 cells are capable of continual growth in a serum-free medium supplemented with transferrin and insulin but with no exogenous mitogenic growth factors. Cells transformed by a mutant of KiMSV that is temperature sensitive for the maintenance of transformation grow in this medium at the permissive temperature only. At the nonpermissive temperature, growth is dependent upon the presence of serum-free conditioned medium from the transformed cells. Normal rat-1 cells are also dependent upon factors from the transformed cells for growth in this serum-free/mitogen-free medium. The serum-derived growth factors, epidermal growth factor, and fibroblast growth factor have no effect on the transformed cells, although epidermal growth factor can replace transforming growth factors produced by KiMSV-transformed cells for the growth of rat-1 cells. Growth of the transformed cells in serum-free medium at clonal densities is dependent upon the presence of conditioned medium collected from the same cells grown to high densities. These results show that (i) growth in serum-free/mitogen-free medium is a general property of KiMSV-transformed cells and (ii) growth of the transformed cells in this medium is dependent upon the presence of growth factors known to be produced by the cells, and they provide support for the hypothesis that serum-free growth of KiMSV-transformed cells is dependent upon ectopically produced growth factors. (Author abstract) (19 Refs)

30. LONG-TERM EPIDERMAL GROWTH FACTOR-RECEPTOR INTERNALIZATION AND PROCESSING IN QUIESCENT HUMAN FIBROBLASTS.

King AC, Cuatrecasas P

Dept. Molecular Biology, Wellcome Res. Lab., Research Triangle Park, NC, 27709

J Supramol Struct Cell Biochem; 17(4):377-387 1981

Long-term internalization and processing of epidermal growth factor (EGF) was studied in quiescent human foreskin fibroblasts (HF). HF were exposed in vitro to unlabeled or 125I-labeled EGF. Pretreatment of HF with 5 nanog (ng) EGF for 2 hr followed by removal of unbound EGF produced no potentiation of DNA synthesis. When EGF was added back to cultures for 14 hr, DNA synthesis was identical to that produced by continuous EGF exposure, suggesting that clearance of cell surface receptors by treatment with EGF does not reduce cellular response to EGF at the concentrations tested. Addition of methylamine (MeNH2), which prevents lysosomal degradation of EGF-recptor complexes, produced an increase in cell-associated EGF compared with controls. This increase was the result of accumulation of EGF within the cells. Cells were apparently able to internalize 125I-EGF even after severe reduction of surface receptors. Max uptake of 125I-EGF in the presence of MeNH2 was 0.27 femtomoles (fmol)/min/culture for untreated cells and 0.019 fmol/min/culture for cells after clearance of surface receptors by pretreatment with EGF. Mitogenic response of fibroblasts to EGF was not reduced by down regulation of surface receptors. (24 Refs)

31. A MONOCLONAL ANTIBODY TECHNIQUE TO DEMONSTRATE AN INCREASE IN LANGERHANS CELLS IN CUTANEOUS LESIONS OF MYCOSIS FUNGOIDES.

MacKie RM

Univ. Dept. Dermatology, Anderson Coll. Building, 56 Dumbarton Road, Glasgow G11 6NU, Scotland

Clin Exp Dermatol; 7(1):43-47 1982

Two monoclonal antibodies raised against cortical thymocytes (NA1 34 and OKT 6) reacted with epidermal Langerhans cells in skin biopsies from six normal subjects. The same antibodies revealed an increased number of Langerhans cells in the epidermis and dermis of 10 biopsies from patients with mycosis fungoides. (15 Refs)

REVIEWS

32. RADIOTHERAPY FOR MALIGNANT MELANOMA: A RE-APPRAISAL.

Harwood AR, Cummings BJ
Dept. Radiation Oncology, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada
Cancer Treat Rev; 8(4):271-282 1981

Indications for radiotherapy (RT) of cutaneous melanoma were evaluated by review of clinical and radiobiological literature, which shows that the disease is not a radioresistant tumor. Indications for RT in lentigo maligna (LM), lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM), and nodular melanomas (NM) are discussed. Results of RT using the Miescher technique and of conventional RT in LM and LMM, results of RT for SSM, results of local excision and postoperative radiation of NM, and results of RT in 0, 7, and 21 fractionated doses, are presented. Fractionated RT plays a substantial role in treatment of LM and LMM, particularly in those of the head and neck. NM arising de novo is not a radioresistant tumor. Evidence suggests that large dose per fraction RT is more effective than conventional RT in the treatment of NM. NM is a tumor with variable radiosensitivity. Local excision and large dose per fraction (4,500 rad in 10 fractions) RT is indicated in NM of the head and neck where wide excision might not be possible or where cosmetic factors are important, in patients with NM following lymph node dissection who are at high risk of developing local or regional recurrence. Such RT produces a high response rate and long-term control of NM recurrent after surgery, or where it is primarily unresectable. Palliative RT is of benefit for relief of symptoms from distant metastases from melanoma. (39 Refs)

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Diagnosis, Treatment

SERIES CT22 No. 82/08
AUGUST, 1982

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DIAGNOSIS

1. ELEVATED GAMMA-GLUTAMYL TRANSPEPTIDASE LEVELS IN MALIGNANT MELANOMA.

Murray JL, Lerner MP, Nordquist RE
Cancer Res. Program, Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, Oklahoma, 73104
Cancer; 49(7):1439-1443 1982

Serum gamma(glutamyl) transpeptidase
measured in 50 patients with malignant m
whether the enzyme was a sensitive ind
Patients were divided into three groups
Eighteen patients, following comple
their primary disease, had a mean GC
national Units/Liter, which was not

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the mean of healthy controls (10.2 +-2.5; range, 5.6-15.2). Likewise, eight patients who had undergone resection of regional disease or solitary metastasis had values near the upper range for controls. Serial testing in 15 of the above patients revealed no significant fluctuations on a daily or monthly basis. In contrast, individuals with metastatic disease has significantly elevated GGTP levels and demonstrated stepwise increases with disease progression. In seven patients enzyme levels were predictive of either recurrent disease or response to therapy. We conclude that serum GGTP levels are a useful test in monitoring clinical status of melanoma patients. (Author abstract) (20 Refs)

2. MALIGNANT MELANOMA OF THE TRUNK: A RETROSPECTIVE REVIEW OF 1,128 PATIENTS.

Ariel IM
Pack Medical Foundation, New York, NY
Cancer; 49(6):1070-1078 1982

Of 3,305 patients with malignant melanoma seen at the Pack Medical Group, New York, during the period from 1935-1975, there were 1,128 (34%) melanomas of the trunk. These cases are discussed. We conclude that melanomas over 1 ml in depth (Breslow's classification), or Levels III, IV and V in Clark-Mihm's classification, elective regional lymph node dissection is warranted. Further studies are necessary to determine the exact treatment procedures for the superficial (Level II) melanomas. Level I melanomas should not be included in a report of metastasizing malignant melanoma. (17 Refs)

3. METASTATIC MELANOMA OF UNKNOWN PRIMARY.

Chang P, Knapper WH
65 East Northfield Road, Livingston, NJ, 07039
Cancer; 49(6):1106-1111 1982

A retrospective study of 166 patients with metastatic melanoma of unknown primary was performed. These were selected from 3,805 cases of melanoma in Memorial Sloan-Kettering Cancer Center from 1949 through 1975 (an incidence of 4.4%). There were 109 male and 57 female patients, 75 with Stage II disease and 91 with Stage III. The site of predominant involvement in Stage II patients was the axilla (47%). Five- and 10 yr survival rates of Stage II patients were 46% and 41%, respectively. The only factor that was shown to influence their survival was the delay (3 mo or more) of radical lymphadenectomy after initial histologic diagnosis. As expected, the prognosis of Stage III patients was very poor. Our study showed that patients with metastatic melanoma of unknown primary followed a similar clinical course as the Stages II and III patients with overt primary lesion. Stage II patients could expect a reasonable survival, the treatment of choice being prompt radical regional lymphadenectomy. (Author abstract) (9 Refs)

4. UVEAL MELANOMA: LOCATION, SIZE, CELL TYPE, AND ENUCLEATION AS RISK FACTORS IN METASTASIS.

McLean IW, Foster WD, Zimmerman LE
Dept. Ophthalmic Pathology, Armed Forces Inst. Pathology, Washington, DC, 20306
Hum Pathol; 13(2):123-132 1982

In this series of 3,432 cases of malignant melanoma of the choroid and ciliary body, mortality from metastasis 15 yr after enucleation was 46%. This mortality was at least 10x greater than has been observed with tumors of the iris, probably owing to the greater size and more malignant cytology of choroidal and ciliary body tumors. In 56% of the 3,432 cases, the melanomas were composed of a mixture of spindle and epithelioid cells. The 15-yr mortality of patients with melanomas of mixed cell type was 3x that of patients with tumors of pure spindle cell type. In 30% of the cases in this series, the melanomas of the choroid and ciliary body were larger than 15 mm in diameter. Size was highly correlated with mortality. The distribution of deaths following enucleation in the 3,432 cases was a log-normal function of time from enucleation. This indicated that metastasis occurred in these fatal cases close to the time of enucleation. The authors were also able to infer that many years were usually required for these uveal melanomas to grow from small (7 to 10 mm in diameter) to large (greater than 15 mm in diameter). These observations are consistent with the hypothesis that dissemination of tumor cells at the time of enucleation has been a major cause of metastasis with small and medium-sized uveal melanomas. (Author abstract) (51 Refs)

5. ELECTRON MICROSCOPIC IDENTIFICATION OF LANGERHANS CELLS IN THE DERMAL INFILTRATES OF MYCOSIS FUNGOIDES.

Jimbow K, Chiba M, Horikoshi T
Dept. Dermatology, Sapporo Medical Coll., Minami 1, Nishi 16, Sapporo 060, Japan
J Invest Dermatol; 78(2):102-107 1982

The importance of the physical interaction between epidermal Langerhans cells and malignant cells in mycosis fungoides (MF) has been stressed recently. To further evaluate the concept, electron microscopic study was carried out to identify whether or not Langerhans cells are also present in the dermal infiltrates of MF. The cells with characteristic Langerhans cell-granules were found in the dermal infiltrates, from early patch to tumor lesions of MF. No vacuolous change suggestive of cell degeneration was found in these cells. These Langerhans cells revealed only a small number of specific granules and nuclear cleavage and chromatin pattern similar to those of malignant lymphoid cells, thus hardly differentiating two cell types in a low power view. Similar to epidermal MF lesions, however, a close apposition of dermal Langerhans cells with malignant lymphoid cells was seen. On one occasion, one Langerhans cell was present at the epidermodermal junction, appearing as being in the process of crossing over the basal lamina. Inasmuch as malignant cells in MF have been shown to possess the functional properties of helper T cells and receptors for Ia (immune associated antigen), expressed in the epidermis solely on Langerhans cells, our findings may further suggest that these malignant T cells bind to Langerhans cells through a 'lock and Key' mechanism involving membrane-bound Ia. (Author abstract) (23 Refs)

6. HUMAN PAPILLOMAVIRUS DNA IN CUTANEOUS PRIMARY AND METASTASIZED SQUAMOUS CELL CARCINOMAS FROM PATIENTS WITH EPIDERMODYSPLASIA VERRUCIFORMIS.

Ostrow RS, Bender M, Niimura M, Seki T, Kawashima M, Pass F, Faras AJ
Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455
Proc Natl Acad Sci USA; 79(5):1634-1638 1982

DNA extracted from squamous cell carcinomas from patients with the chronic wart disease syndrome, epidermodysplasia verruciformis, was analyzed for the presence of human papillomavirus (HPV)-specific DNA sequences by Southern blot hybridization analysis. Employing an HPV probe obtained by molecular cloning of viral DNA purified from benign warts from these patients, we have unequivocally identified HPV-specific nucleotide sequences in squamous cell carcinomas from these patients. Restriction endonuclease mapping indicated that the DNA present in the carcinomas was of the same type (Type 5) as that found in the benign tumors from these patients and was present as unintegrated, free viral DNA. Moreover, we have demonstrated the presence of HPV-5 DNA in a subcutaneous metastatic tumor from one of these patients. This latter observation essentially eliminates the possibility that the HPV-5 DNA present in the malignant tumors in these patients resulted from cross-contamination from an adjacent benign warty lesion. In addition to wild-type HPV-5 DNA, both the primary and metastatic carcinomas analyzed also contained an HPV-5 DNA species lacking approximately 20% of the HPV-5 DNA genome. These subgenomic forms of HPV-5 DNA could not be detected in benign papillomas from these patients. (Author abstract) (25 Refs)

7. CORRELATION BETWEEN HUMAN PAPILLOMAVIRUS (HPV) TYPE AND HISTOLOGY OF WARTS.

Gross G, Pfister H, Hagedorn M, Gissmann L
Universitats-Hautklinik Freiburg, Hauptstrasse 7, 7800 Freiburg i Br., W. Germany
J Invest Dermatol; 78(2):160-164 1982

Forty warts from different patients and of different clinical type were examined histologically and virologically. Eight lesions were found to be associated with human papillomavirus Type 1 (HPV 1), 15 tumors were induced by HPV 2, HPV 3 was detected 4 times, HPV 4 twice, and HPV 6 11 times. HPV3, HPV 4, and HPV 6 induced warts revealed a correlation between histology and virus type. They are characterized by the so called 'edematous type clear cells'. In HPV 3 associated flat warts pycnotic nuclei were mainly localized in the center of large vacuoles. In genital warts sickle shaped nuclei were pushed to the margin of the vacuolized cells. The histology of HPV 1 and HPV 2 induced warts was more heterogenous. With one exception HPV 1-induced lesions represented typical myrmecia warts, varying in the number and shape of inclusion bodies. HPV 2 associated common warts, however, revealed three very distinct histologic features: (1) inclusion wart typical for HPV 1; (2) classical common wart with marked condensation of keratohyalin granules; (3) warts with extreme vacuolization of squamous and granular cells leading to a honeycomb-like picture. (Author abstract) (25 Refs)

8. BETA2-MICROGLOBULIN IN SKIN CANCER.

Dahl MV
Minneapolis, MN
J Am Acad Dermatol; 5(6):698-699 1981

Use of beta2-microglobulin (b-MG) as a marker for histologic diagnosis of malignant skin lesions and for assessing whether a lesion has been completely excised is proposed. b-MG was found in 6/6 basal cell papillomas, 0/6 basal cell carcinomas, 3/6 squamous cell carcinomas, 5/6 lesions of Bowen's disease, and 5/5 melanomas. Further studies to support these findings and to elucidate specific changes of cell surface receptors associated with malignancy are warranted. (6 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

9. IMMUNODIAGNOSIS OF HUMAN MELANOMA: CHARACTERIZATION OF HUMAN MELANOMA ANTIGENS AND THEIR DETECTION IN SERA OF MELANOMA PATIENTS BY RADIOIMMUNOASSAY.

Ishii Y, Mavligit GM
Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan
Oncology; 39(1):23-28 1982

Double antibody radioimmunoassay (RIA), using radioiodinated melanoma-associated antigens (MAA), rabbit antiserum raised against 3 M KCl extract of human melanoma (AHMS) and goat antirabbit IgG antibody, was employed for the detection of MAA in tumors as well as in sera of melanoma patients. MAA were partially purified from crude KCl extract of melanoma tissue by affinity column chromatography using AHMS and concanavalin A. A high content of MAA was detected in all but one melanoma extract, while normal tissue and nonmelanoma tumor extracts contained MAA to a much lesser extent than did melanoma extracts. MAA were also found in melanoma patients' sera (20/45) but not in sera of normal donors (0/10) and colon cancer patients (0/10). Immunochemical data suggest that AHMS-defined MAA consist of two major glycoproteins with mol wt of 37K and 31K daltons, which does not cross-react either with carcinoembryonic antigen or beta2-microglobulin or with BCG. (Author abstract) (29 Refs)

10. EFFECT OF SYSTEMIC INTERFERON ON NATURAL KILLER CELL FUNCTION IN MELANOMA PATIENTS.

Golub SH, Burk M
Univ. California Los Angeles, Los Angeles, CA
UCLA Cancer Cent Bull; 9(1):3-6 1982

The effect of human leukocyte interferon on natural killer (NK) cell function was examined in patients with disseminated malignant melanoma. Treatment of 16 patients with human leukocyte interferon was not associated with any notable change in the proportion or absolute number of major lymphocyte subpopulations, including T and B cells and Fc receptor cells. When NK activity was tested against the myeloid leukemia target K562, NK activity declined at 24 hr after the first administration of interferon. Subsequently, activity rose, with peak activity found at 7 days of continuous daily treatment. When five patients who may have had some clinical benefit from interferon treatment were compared with four patients with rapid disease progression, no difference in the degree to which NK cytotoxicity was augmented by interferon was seen. Results of cellular analysis suggested that in vivo treatment with interferon results in both an increase in cytotoxicity by mature NK cells and recruitment of additional cells from precursors of NK cells into the NK differentiation pathway. (7 Refs)

11. A RANDOMIZED PROSPECTIVE CLINICAL TRIAL OF ADJUVANT C. PARVUM IMMUNOTHERAPY IN 260 PATIENTS WITH CLINICALLY LOCALIZED MELANOMA (STAGE I): PROGNOSTIC FACTORS ANALYSIS AND PRELIMINARY RESULTS OF IMMUNOTHERAPY.

Balch CM, Smalley RV, Bartolucci AA, Burns D, Presant CA, Durant JR, Southeastern Cancer Study Group
Dept. Surgery, Univ. Alabama in Birmingham, University Station, Birmingham, AL, 35294
Cancer; 49(6):1079-1084 1982

A total of 260 patients with clinically localized melanoma (Stage I) from 18 medical institutions in the Southeastern Cancer Study Group were randomized to receive either surgical treatment alone, or surgery plus Corynebacterium parvum immunotherapy. A multivariant analysis (Cox regression model) of nine prognostic factors was performed on 110 patients with a minimum of 2 yr follow-up. The dominant prognostic variables were thickness ($p = 0.0007$) and anatomic location of the melanoma (trunk vs other, $p = 0.015$). Disease-free survival curves were than calculated for 204 surgically evaluable patients. It is concluded that a prognostic factors analysis is critically important in adjunctive trials of melanoma to determine which dominant variables should be used for analyzing patient subgroups; that C parvum immunotherapy appears to be associated with an improved disease-free survival rate in the subgroup of patients with melanomas greater than 3 mm thickness (this early encouraging data must still be confirmed with continued patients accrual and a longer observation period); and that patients with melanomas less than 3 mm thick have a relatively favorable prognosis after appropriate surgical treatment, and immunotherapy does not improve their survival rates. (24 Refs)

12. THE RELATIONSHIP BETWEEN T LYMPHOCYTE SUBSETS AND IA-LIKE ANTIGEN POSITIVE NONLYMPHOID CELLS IN EARLY STAGES OF CUTANEOUS T CELL LYMPHOMA.

Thomas JA, Janossy G, Path MR, Graham-Brown RA, Kung PC, Goldstein G
Dept. Immunology, Royal Free Hosp. Sch. Medicine, Pond St., London NW3 2QG, England
J Invest Dermatol; 78(2):169-176 1982

Immunofluorescence studies were carried out in cutaneous T cell lymphoma (mycosis fungoides) in order to analyze the microanatomical relationship of the different T lymphocyte subsets (inducer and suppressor/cytotoxic cell populations) to large nonlymphoid Langerhans-type and so-called 'indeterminate' or interdigitating cells. The conventional and mouse (monoclonal) antibodies were used in various combinations using fluorescein and rhodamine labeled second layers. In five of the seven cases studied the dermal infiltrate consisted of numerous T (HuTLA+) lymphocytes, 80-90% of which expressed the inducer phenotype (HuTLA+,OKT4+). Most of these cells formed close contact with large cells exhibiting large amounts of Ia-like antigens. These cells corresponded to the interdigitating and indeterminate cells in the sections. By contrast, only small numbers (10-20%) of T cells of suppressor/cytotoxic type (HuTLA+,OKT8+) were seen. These did not show a close affinity to the Ia-like antigen positive nonlymphoid component but appeared to have a predilection for the epidermis. Epidermal Langerhans cells, also strongly Ia-like antigen positive, were further defined by two monoclonal antibodies reacting with a cortical thymocyte antigen HTA-1. Although Langerhans cells are probably related to the Ia-like antigen positive dermal cells only a few of the abundant latter population were HTA-1+. In the remaining two cases, larger populations of OKT8+ (suppressor/cytotoxic) cells were seen and could be heralding a particularly benign course. These observations indicate a close functional relationship between the lymphoid and Ia-like antigen positive dermal cells during the pre-malignant phase of cutaneous T cell lymphoma. (Author abstract) (39 Refs)

13. AMYL NITRITE MAY ALTER T LYMPHOCYTES IN HOMOSEXUAL MEN.

Goedert JJ, Wallen WC, Mann DL, Strong DM, Neuland CY, Greene MH, Murray C, Fraumeni JF, Blattner WA
Environmental Epidemiology Branch, NCI, Landow Building - Room 4C18, Bethesda, MD, 20205
Lancet; 1(8269):412-416 1982

To evaluate the recent outbreak of Kaposi's sarcoma (KS) and opportunistic infections in homosexual men, clinical, virological, and immunological data on 2 homosexual men with KS and on 15 healthy homosexual volunteers were collected. Both KS patients had regularly used amyl nitrite or butyl nitrite (AN); they had low helper/suppressor (H/S) T lymphocyte ratios before chemotherapy and high titers of antibody against cytomegalovirus (CMV). Eight of the 15 volunteers were regular AN users; 7 of the 8 had low H/S ratios due to larger than normal numbers of OKT8-positive suppressor cells and smaller numbers of OKT4-positive helper cells. In all eight AN users the fluorescence profile obtained with monoclonal antibody 9.6 (which detects the sheep E-rosette receptor) was bimodal, indicating a subpopulation of T cells with increased receptor density. A similar pattern was observed when OKT8, the antibody which detects cytotoxic suppressor cells, was used. Two of the seven men who did not use AN had abnormal fluorescence with reagent 9.6, and one of these also had a low H/S ratio. CMV-antibody titers were persistently high in 14 of the 15 healthy men, but the titers were not related to An use or T-cell abnormalities. The data suggest that nitrites may be immunosuppressive in the setting of repeated viral antigenic stimulation and may contribute to the high frequency of KS and opportunistic infections in homosexual men. (Author abstract) (35 Refs)

CHEMOTHERAPY

14. PHASE II STUDY OF HIGH-DOSE TAMOXIFEN (NSC-180973) IN PATIENTS WITH DISSEMINATED MALIGNANT MELANOMA.

Creagan ET, Ingle JN, Ahmann DL, Green SJ
Mayo Clinic, Rochester, MN, 55901
Cancer; 49(7):1353-1354 1982

Seventeen patients with disseminated malignant melanoma received a daily oral regimen of tamoxifen, 100 mg/m2. All patients had prior chemotherapy and predominantly visceral involvement. None of the patients had an objective regression, and most (71%) had progressive disease at the time of first reassessment. Moderate to severe nausea occurred in 24% of patients. In the dose and schedule used in this study, tamoxifen is ineffective in patients with advanced malignant melanoma and prior chemotherapy exposure. (Author abstract) (18 Refs)

15. PILOT STUDIES USING MELANOMA TUMOR-ASSOCIATED ANTIGENS (TAA) IN SPECIFIC-ACTIVE IMMUNOCHEMOTHERAPY OF MALIGNANT MELANOMA.

Hollinshead A, Arlen M, Yonemoto R, Cohen M, Tanner K, Kundin WD, Scherrer J
Dept. Medicine, George Washington Univ. Medical Center, 2300 I St., N.W., Washington, DC, 20037
Cancer; 49(7):1387-1404 1982

Highly purified melanoma TAA which induce melanoma-related cell-mediated immune responses have been further characterized using hyperimmune TAA antisera after affinity chromatography for double immunodiffusion-immunoelectrophoresis and indirect immunofluorescence studies. An additional study of antigenic modulation was performed in 23 nonanergic and seven anergic melanoma patients, tested simultaneously with melanoma TAA prepared from primary and metastatic tumors, which had been obtained from one patient at different time periods. The results of pilot clinical trials are reported, including toxicity, timing and dosage studies in 20 patients and subsequent studies of patients with metastatic melanoma treated at three separate centers, using a single lot of purified, allogeneic melanoma TAA. The results of these latter studies in 51 patients with Stage III (distantly metastatic) melanoma and in five patients with earlier stages of disease indicate that: (1) when the interval from primary therapy to recurrence is greater than 1 yr and when liver, bone and brain are not involved, partial or total clinical regression may be noted in up to 25% of patients with metastatic disease receiving immunochemotherapy; (2) when total regression does occur, the effect usually lasts from 1 to 3 yr; (3) cytoreductive (debulking) surgery, when possible, in cutaneous, nodal retroperitoneal, and visceral regions may enhance the response to specific active immunochemotherapy, although some debulked patients had less tumor burden, and this factor alone may lead to an improved prognosis in patients undergoing any subsequently treatment; (4) when circulating inhibitory factors are modified through preimmunization chemotherapy, an enhanced host response may be seen; and (5) Cancer Serum Indices (CSI) may be useful in predicting recurrence and in following tumor load and response to therapy. Information obtained from these studies suggests the need for further trials to determine the effect of immunization on patients with earlier stages of disease where recurrence rates remain high, and to evaluate the mechanisms of tumor rejection or tumor progression in the face of immune stimulation. (Author abstract) (32 Refs)

16. TRIAL OF AN AROMATIC RETINOID IN PATIENTS WITH SOLID TUMOURS.

Rustin GJ, Bagshawe KD
Dept. Medical Oncology, Charing Cross Hosp., Fulham Palace Road, London W6 8RF, England
Br J Cancer; 45(2).304-308 1982

Twenty-four patients with various solid tumors refractory to conventional treatment were treated with etretinate (ETR; a synthetic aromatic retinoid). Initially a dose of 100 mg/day caused hypervitaminosis A, and the dosage was reduced to 25-50 mg/day. Nineteen of the cases were evaluable, the patients having received ETR for at least 4 wk. Disease progression was observed in 17 patients and static disease in 2. No disease progression was observed in a patient with adenocarcinoma of the lung; however, the patient died suddenly after 6 wk of treatment. A patient with metastatic melanoma (multiple cerebral) showed no disease progression; initial treatment was excision followed by cranial irradiation and lomustine. Two patients with advanced ovarian adenocarcinoma had stabilization of disease for 12 and 17 wk, but disease progressed at 17 and 21 wk, respectively. In the six patients with testicular teratomas, ETR did not induce differentiation of the tumors; one patient had an undifferentiated active teratoma after 9 wk of therapy with ETR, while the other five had tumor enlargement and a rise in tumor markers while taking ETR. A trial of ETR for patients with melanoma may be useful, because the drug has minimal toxicity and no successful treatments exist for the disease. (14 Refs)

17. THERMOCHEMOTHERAPY FOR MELANOMA METASTASES IN LIVER.

Storm FK, Kaiser LR, Goodnight JE, Harrison WH, Elliott RS, Gomes AS, Morton DL
540-140 CHS, Univ. California, Los Angeles, CA, 90024
Cancer; 49(6):1243-1248 1982

Metastatic melanoma in the liver has carried an extremely poor prognosis regardless of therapy. Because transient responses (1/6 disease regressions and 2/6 disease stabilizations for 4 mo) in selected patients treated with intraarterial (IA) DTIC infusion were encouraging and because localized hyperthermia may be both tumoricidal and synergistic with chemotherapy, these modalities were combined for treatment of patients with advanced liver metastases. Of 10 patients treated with IA-DTIC plus heat, 3 (30%) had disease regression and 5 (50%) had disease stabilization for 3-14 mo (median 6.5 mo) and survived 2.5-18 mo (median 8.5 mo). During treatment, 4/5 patients had pain relief and 7/10 retained or acquired normal activities. Myelosuppression was minimal and no hyperthermia toxicity occurred. A retrospective review of 10 patients with similar disease levels who were treated with conventional intravenous (IV)-DTIC indicated no responses, and no responses were seen in 5 patients treated with IV-DTIC plus heat. However, this latter group may have been selected patients due to the inability to place a percutaneous hepatic artery infusion catheter. This pilot study suggests that combination IA-DTIC and hyperthermia has a high response rate, is safe, and can provide quality survival for many patients. (Author abstract) (11 Refs)

RADIOTHERAPY

18. IS THE MALIGNANT MELANOMA REALLY RADIOTHERAPY-RESISTANT?.

Storck H
Mittelbergsteig 7b, CH-8044 Zurich, Switzerland
Hautarzt; 33(1):5-11 1982

Radiation treatment of malignant melanoma (MM), results of MM radiation treatment since 1971, experiments with animal MM, MM radiosensitivity measured in in vitro experimental conditions, and possibilities of intensification of the radiation effect on MM are reviewed. The 5-yr survival rate from a collective study for 1,749 patients with MM Stage I is 67% for a single irradiation, 50% after surgery, 66% after radiation therapy and surgery, and 45% after radiation treatment following surgery. Difficulties in evaluation of MM treatment, with or without statistical interpretation, are due to the fact that single dose irradiation and fractionated irradiation are comparable only partially in their efficacy according to the duration and dosage of the fractions. The clinical radiosensitivity of human MM can be compared with the experimental hamster or mice melanoma, or with the sensitivity of cultured melanoma cells. Clinical experience, animal experiments, and culturing procedures revealed no evidence concerning the radiotherapy-resistance of MM. Application of the time-dosage-fraction (TDF) factors according to Orton and Ellis enables the comparison of biological effects for different TDF schedules. Electroaffine sensitizers, fast electrons, or neutrons with high linear energy transfer and small oxygen enhancement ratio could increase the efficiency of MM radiotherapy. (43 Refs) (In GER)

SURGERY

19. PROPHYLACTIC LYMPH NODE DISSECTION IN CLINICAL STAGE I CUTANEOUS MALIGNANT MELANOMA: RESULTS OF SURGICAL TREATMENT IN 1319 PATIENTS.

Milton GW, Shaw HM, McCarthy WH, Pearson L, Balch CM, Soong SJ
(c/o Shaw) Melanoma Clinic, Sydney Hosp., Macquarie St., Sydney 2000, Australia
Br J Surg; 69(2):108-111 1982

A retrospective study was made of 1,319 patients with cutaneous primary malignant melanoma and regional lymph nodes clinically free of disease, whose first definitive surgical treatment was either (a) wide excision of the primary lesion (WE) or (b) wide excision of the primary lesion plus a prophylactic lymph node dissection (PLND). Patients were stratified according to three dominant prognostic factors, as revealed by multifactorial analyses: sex of patient, the anatomical site and thickness of the primary lesion. Of 380 patients who underwent PLND for lymph nodes clinically free of disease, there was microscopic evidence of nodal metastases in 5%. Despite this, prognosis in these patients was nearly twice as good as in those patients undergoing lymph node dissection for clinically involved nodes. Five-yr survival rates for all those clinical Stage I patients with lesions less than 0.8 mm thick were high irrespective of initial surgical treatment. In men with lesions of intermediate thickness (particularly 1.6-3.0 mm), survival rates for those undergoing PLND were considerably higher than for those undergoing WE. There were no survival benefits of PLND in men with lesions thicker than 3.0 mm. This was in contrast to the situation in women, where PLND was indicated for patients with the thickest lesions. This study has defined three parameters which can serve as useful practical guides for selecting alternative surgical procedures in the management of clinical Stage I cutaneous malignant melanoma. (Author abstract) (22 Refs)

MULTIMODAL THERAPY

20. TREATMENT OF MYCOSIS FUNGOIDES. TOTAL-SKIN ELECTRON-BEAM IRRADIATION VS TOPICAL MECHLORETHAMINE THERAPY.

Hamminga B, Noordijk EM, Van Vloten WA
Dept. Dermatology, Univ. Hosp., Rijnsburgerweg 10, 2333AA Leiden, The Netherlands
Arch Dermatol; 118(3):150-153 1982

Of 42 patients who had mycosis fungoides (MF) confined to the skin with or without dermatopathic lymphadenopathy, 21 were treated with topically applied mechlorethamine hydrochloride and 21 with total-skin electron-beam irradiation. The results of both therapeutic modalities are compared. We conclude that in the early stage of the disease, both forms of treatment are equally effective. In the later stages of MF, in the absence of lymph node or other systemic involvement, electron-beam irradiation seems to be superior in inducing an initial complete remission. However, because of the large number of patients who have a relapse after this therapy, it should be followed by topical mechlorethamine therapy. (Author abstract) (14 Refs)

CASE REPORTS

21. AN AMELANOTIC MELANOMA TRANSFORMED INTO MELANOTIC MELANOMA WITH DEVELOPMENT OF VITILIGO.

Takematsu H, Tomita Y, Sato A, Seiji M
Dept. Dermatology, Tohoku Univ. Sch. Medicine, 1-1 Seiryomachi, Sendai 980, Japan
J Dermatol (Tokyo); 8(6):431-438 1981

The case of a 77-yr-old woman with amelanotic melanoma which transformed into melanotic melanoma after chemotherapy is reported. The patient has a history of melanoma of the right second toe since her twenties. The lesion gradually increased in size; the lesion was excised and lymph nodes in the right inguinal region were dissected when the patient was 67 yr old. At the age of 75, the patient noticed swelling in the right popliteal, inguinal, and axillary regions. At the present admission, the patient had multiple, round, raised, well-marginated, skin-colored lesions on the right external genitalia and a raised sc tumor on the abdomen. Right axillary and inguinal nodes were enlarged. Vitiligo was present in an area around the metastatic sc tumor and on the lower right extremity. Multiple lung masses were seen on plain films. Computed tomography demonstrated a large mass in the right occipital region. Three treatments with dacarbazine, aminochloroethyl nitrosourea, and vincristine reduced the sizes of the lesions; however, the tumors became unresponsive thereafter, increased in size, became pigmented and bled easily. The patient's condition deteriorated and she died 2 yr after admission. It is suggested that the chemotherapy led to the appearance of the melanotic melanoma cells. (9 Refs)

22. DIFFUSE MELANOSIS SECONDARY TO METASTATIC MALIGNANT MELANOMA: LIGHT AND ELECTRON MICROSCOPIC FINDINGS.

Adrian RM, Murphy GF, Sato S, Granstein RD, Fitzpatrick TB, Sober AJ
(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114
J Am Acad Dermatol; 5(3):308-318 1981

A case of diffuse melanosis in a patient with malignant melanoma (MM) is reported. Hyperpigmented skin, not grossly involved by MM, was examined by light and electron microscopy. Slate blue color pigmentation of the skin was attributed to deposition of melanin in perivascular dermal macrophages. No intact melanosomes or metastases of MM were found in clinically normal skin. The role of metastases in dermal pigmentation is apparently less important than previously thought. (16 Refs)

23. KAPOSI'S SARCOMA IN A PATIENT WITH DERMATOMYOSITIS RECEIVING IMMUNOSUPPRESSIVE THERAPY.

Weiss VC, Serushan M

Dept. Dermatology, Univ. Illinois Medical Center, P.O. Box 6998, Chicago, IL, 60680

Arch Dermatol; 118(3):183-185 1982

Kaposi's sarcoma occurred in a 65-yr-old Mexican woman who had been treated for dermatomyositis with prednisone for 2 1/2 yr and with azathioprine for 4 mo. Kaposi's sarcoma, a malignant neoplasm not usually associated with dermatomyositis, may be a consequence of immunosuppressive therapy in this patient. (Author abstract) (17 Refs)

24. PSORIASIS AND THE RISK OF CANCER.

Stern R, Zierler S, Parrish JA

Dept. Dermatology, Beth Israel Hosp., 330 Brookline Ave., Boston, MA, 02215

J Invest Dermatol; 78(2):147-149 1982

To test the validity of the common hypothesis that patients with psoriasis have an inherently lower susceptibility to cancer, we prospectively studied 1,367 patients with severe psoriasis who enrolled in a clinical trial of oral methoxsalen photochemotherapy for treatment of psoriasis for an av of 3.2 yr. The incidence of non-cutaneous cancers and the number of deaths from such cancers were slightly but not significantly higher than that expected for the general population (relative risk = 1.1; standard mortality ratio = 1.3). Among 318 patients (23%) in this cohort who were over 35 yr of age and who lacked appreciable exposure to suspected cutaneous carcinogens, the observed incidence for cutaneous carcinoma was 1.4 times that expected, based on rates for the general population (90% confidence interval = 0.8 to 2.7). These data suggest that patients with psoriasis have a risk of systemic and cutaneous cancer that is comparable to the risk for the general population. (Author abstract) (17 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

25. MELANOMA IN BLACK PATIENTS.

Smith RJ

Medical-Dental Associates Building, 617 Cherry St., Pine Bluff, AR, 71601

J Natl Med Assoc; 74(4):377-383 1982

Melanoma in black patients is uncommon but not rare. This paper reports six cases seen in one general surgeon's practice in Arkansas during a 14-yr period. A review of the current literature regarding melanoma in blacks is given. Characteristically, melanoma in blacks is found on the soles of the feet, palms of the hands, or mucous membranes. The tumor has a deadly potential unless it is treated at an early stage; four of the patients reported have died of metastatic disease. A public health program is needed to make physicians and the public aware of the incidence and location of this tumor. (Author abstract) (18 Refs)

26. CANCER OF THE SKIN IN BLACKS. I. A REVIEW OF 163 BLACK PATIENTS WITH CUTANEOUS SQUAMOUS CELL CARCINOMA.

Mora RG, Perniciaro C

Dept. Dermatology, L.S.U. Sch. Medicine, 1542 Tulane Ave., New Orleans, LA, 70112

J Am Acad Dermatol; 5(5):535-543 1981

Age and sex distribution, predisposing conditions, anatomic site, and mortality were considered for squamous cell carcinoma (SCC) of the skin in 163 blacks (81 men, 82 women; 11-100 yr old). Eleven patients had multiple tumors. The total number of SCC was 176. The most common predisposing conditions were scarring processes. Seven SCC arose from burn scars. In six patients, the SCC arose from chronic leg ulcers. The av duration of ulceration was 8.6 yr before diagnosis of SCC. Other diseases associated with scarring included: hidradenitis suppurativa (2 cases), granuloma inguinale (1), lymphogranuloma venereum (1), discoid lupus erythematosus (1), and lupus vulgaris (1). The largest number of tumors for both men and women occurred on the face and the lower extremities. The scalp was a significant site in women. The back and neck were uncommon locations in both sexes. Of the 163 black patients with skin SCC, 30 (15 men, 15 women) are known to have died as a direct result of SCC from either metastasis or local extension. The overall death rate was 18.4%. (11 Refs)

27. SOLAR RADIATION AND MALIGNANT MELANOMA OF THE SKIN.

Houghton AN, Viola MV

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

J Am Acad Dermatol; 5(4):477-483 1981

Solar radiation is discussed in relation to the pathogenesis of malignant melanomas (MM) of the skin. The incidence of MM in relatively homogeneous white populations in North America, northern Europe, and Australia is inversely proportional to latitude. MM tends to occur on sites more heavily exposed to sun during recreation. MM is more likely to develop in lightly pigmented individuals. Susceptible persons who have lived in a sunny climate all of their lives have a higher incidence of MM than persons who have recently moved to the same area from less sunny climates. A higher incidence of MM seems to occur in areas with extensive coastlines. MM is more frequent in the summer. MM rates are considered in terms of indoor and outdoor occupations. Sunspot cycles seem to be correlated with subsequent increases in MM incidence rates. Max sunspot numbers coincide with periods of increased solar activity. The rise in MM incidence 0-3 yr after sunspot peaks suggests that heavier exposures to UV radiation trigger the clinical appearance of MM. Solar radiation is considered as a dose-dependent carcinogen and as a cocarcinogen or promoter. (34 Refs)

SELECTED PRECLINICAL STUDIES

28. A NEW MELANOMA SEEKER FOR POSSIBLE CLINICAL USE: SELECTIVE ACCUMULATION OF RADIOLABELLED THIOURACIL.

Dencker L, Larsson B, Olander K, Ullberg S
Dept. Toxicology, Univ. Uppsala, Uppsala, Sweden
Br J Cancer; 45(1):95-104 1982

In a previous report we have shown that a few substances, especially thiouracil, are incorporated as false precursors into melanin during its synthesis. In the present investigation, we have intensified our studies on the incorporation of thiouracil into melanotic melanomas Firstly, the distribution and retention of both 14C- and 35S-labeled thiouracil in mice with transplanted melanomas were studied . A high and selective accumulation was found in the melanotic tumors. The concentration in the rest of the body was low, with the exception of the thyroid gland. Secondly, melanoma-bearing mice were given increasing doses of thiouracil, and cultured melanoma cells were exposed to different concentrations of thiouracil, to investigated the relation between dose and uptake in melanomas and melanoma cells, respectively. A relatively linear increase in uptake with dose was found, indicating that the melanin incorporation of thiouracil is non-saturable up to subtoxic levels. (Author abstract) (12 Refs)

29. ANTIBODY-INDUCED RELEASE OF CELLULAR PROTEINASES: LOSS OF ADHESION OF HUMAN MELANOMA CELLS AFTER BINDING OF ANTI-MELANOMA ANTIBODY.

Singer KH, Hashimoto K, Stuhlmiller GM, Lazarus GS
Duke Univ. Medical Center, Box 2987, Durham, NC, 22710
J Immunol; 128(3):1321-1326 1982

Incubation of monolayer cultures of human melanoma cells with monkey anti-human melanoma IgG resulted in loss of cellular adhesion. Release of melanoma cells from the culture dish was not the result of cytotoxicity. Antibody-induced cell detachment was partially inhibited by the addition of diisopropylfluorophosphate (DFP), and detachment was completely inhibited by the addition of lima bean trypsin inhibitor. Thiol and carboxyl proteinase inhibitors did not block antibody-induced cellular detachment. An IgG dose-dependent increase in DFP-inhibitable caseinolytic activity was demonstrated in the culture medium of melanoma cells incubated with anti-melanoma IgG, but not in those incubated with normal monkey IgG. Medium collected from antibody-treated cell cultures and incubated with protein A-Sepharose to remove IgG caused detachment of melanoma cells in fresh cultures. Preincubation of this conditioned medium from antibody-treated cell cultures with DFP abolished the medium's ability to mediate loss of cellular adhesion. These data suggest that incubation of melanoma cells with immune IgG results in release of a serine proteinase that mediates cellular detachment. (Author abstract) (36 Refs)

30. CATHEPSIN B ACTIVITY IN B16 MELANOMA CELLS: A POSSIBLE MARKER FOR METASTATIC POTENTIAL.

Sloane BF, Honn KV, Sadler JG, Turner WA, Kimpson JJ, Taylor JD
Dept. Pharmacology, Wayne State Univ., 540 E. Canfield, Detroit, MI, 48201
Cancer Res; 42(3):980-986 1982

In solid sc tumors of a variant of the murine B16 melanoma with high metastatic potential (B16F10), there was a two- to seven-fold elevation of lysosomal cathepsin B activity when compared to the B16F1 variant with low metastatic potential. The highest activities (based on either protein or DNA) of cathepsin B were found in tumors of less than 1 g. When B16F1 and B16F10 melanoma variants were grown in tissue culture, the metastatic differential in cathepsin B activity was lost as the cells were subcultured. How ever, this differential in cathepsin B activity could be restored by reestablishing the cultured cells as sc tumors. The activities of four other lysosomal enzymes (cathepsin D, beta-N-acetylglucosaminidase, beta-glucuronidase, and acid phosphatase) showed little evidence of a positive correlation with the metastatic potential of the B16 melanoma variants Eighty to 90% of cathepsin B activity has been localized to a fraction containing viable tumor cells which was isolated by centrifugal elutriation. In contrast, only 50% of cathepsin D activity was in the viable tumor cell fraction, and from 30 to 70% of beta-N-acetylglucosaminidase, beta-glucuronidase, and acid phosphatase. Elevated levels of cathepsin B in the high metastatic B16F10 varient are consistent with the idea that cathepsin B may play a direct or a regulatory role in tumor metastasis. (Author abstract) (41 Refs)

31. ANIMAL MODEL OF INTRACUTANEOUS MELANOMA.

Levine N, Queen L, Chalom AA, Daniels LJ
Section Dermatology, Univ. Arizona Health Sciences Center, Tucson, AZ, 85724
J Invest Dermatol; 78(3):191-193 1982

An animal model which allows for the implantation and development of intracutaneous melanoma is described. Intradermal vesicles are created by a negative pressure apparatus in DBA/2J mice. S91 melanoma cells are injected into the blister cavities. Tumor growth occurs within 7 days and the yield approaches 100%. This model is a rapid, efficient, and applicable system for the study of melanoma growth dynamics and of the effects of systemic and topical anti-tumor agents on melanoma proliferation. (Author abstract) (12 Refs)

32. EFFECTS OF DOPAMINE AGONISTS AND ANTAGONISTS ON MURINE MELANOMA: CORRELATION WITH DOPAMINE BINDING ACTIVITY.

Krummel TM, Neifeld JP, Taub RN
(c/o Nefeld), Medical Coll. Virginia, P.O. Box 11, MCV Station, Richmond, VA, 23298
Cancer; 49(6):1178-1184 1982

The biosynthetic pathway producing melanin is present in many melanomas. Previous investigations have suggested that pharmacologic levels of intermediates in this pathway (L-dopa, dopamine, and their analogues) may inhibit macromolecular synthesis in some tissue culture melanoma cell lines and prolong survival in tumor-bearing mice. Recently, a potent antidopamine drug (pimozide) has been developed. This study was designed to investigate the effects of these drugs on murine melanomas and to correlate effect on macromolecular synthesis with competitive dopamine binding activity (receptors) and melanin synthesis. Three murine melanomas (F1, F10, B16) were studied. The amelanotic B16 cell line showed no inhibition by dopa, dopamine, or pimozide when assayed for 14C-leu or 3H-TdR incorporation. Using a competitive binding assay, only low levels of dopamine binding were present. The very melanotic F1 cell line showed no inhibition by dopa or dopamine, but pimozide inhibited 14C-leu and 3H-TdR incorporation in a dose-response fashion; 50% inhibition was noted at 10(-9) M concentration with no loss in cell viability as tested by trypan blue exclusion or cell counting. Competitive dopamine binding was present (19 pmoles per g of wet tissue) with a Kd of 0.2 nM, figures approximating those seen in normal dog caudate nucleus controls. The F10 line, with melanin production between the B16 and F1, was intermediate in terms of inhibition of 14C-leu and 3H-TdR incorporation and dopamine binding. Purified melanin did not bind and, thus, does not appear to explain these binding results. These data suggest that pimozide, a drug which is a potent dopamine antagonist, may inhibit 14C-leu and 3H-TdR incorporation in murine melanoma cells and that competitive dopamine binding (receptor) appears to correlate with this inhibition. This drug and the dopamine binding assay may be useful in the study of human melanoma. (Author abstract) (15 Refs)

33. PRODUCTION OF HUMAN ALPHA1-ANTICHYMOTRYPSIN-LIKE PROTEIN BY A HUMAN MALIGNANT MELANOMA TRANSPLANTED INTO NUDE MICE.

Kondo Y, Ohsawa N
Ludwig Inst. Cancer Res., Royal Melbourne Hosp., Post Office, Victoria 3050, Australia
Cancer Res; 42(4):1549-1554 1982

A tissue culture line of a human malignant melanoma, SEKI, induced cachexia in nude mice (BALB/c-nu/nu). During the investigation of the cause of the cachexia, the melanoma was found to produce a protein immunologically identical to human alpha1-antichymotrypsin (alpha1-Ach). Tissues of the SEKI melanoma contained the protein immunologically equivalent to 0.29 +-0.11 (SD) mg of human alpha1-Ach per g of wet tissue, while the other six human malignant tumors transplanted into nude mice did not contain a detectable amount of it. In the serum of nude mice bearing the melanoma, this protein appeared soon after the tumor growth occurred and gradually increased up to the level equivalent to 5 mg of human alpha1-Ach per dl. Removal of the tumor resulted in a rapid decrease of the protein in the serum to an undetectable level within 1 day. This protein was never detected in the serum of nude mice bearing the other 27 human malignant tumors or controls. Purification of this protein was carried out by the column chromatography using DE-52, Blue-Sepharose, and SP-Sephadex. The elution patterns were the same as those of alpha1-Ach in human serum, and the mol wt of the protein was estimated as 69,000 by Sephadex G-100 column chromatography and 65,000 by polyacrylamide gel electrophoresis with sodium dodecyl sulfate. This purified protein, however, did not exhibit inhibitory activity against chymotrypsin. These results show that this melanoma produced a protein immunologically identical and physicochemically very similar to human alpha1-Ach. This melanoma-nude mouse system may provide a useful model for investigating the synthesis of human alpha1-Ach and analysis of its physiological roles. (Author abstract) (20 Refs)

34. RESISTANCE TO ULTRAVIOLET RADIATION IN HUMAN MELANOMA CELLS.

Konishi T
Second Dept. Internal Medicine, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 31(1):15-27 1981

Sensitivities of four malignant melanoma (MM) cell lines, MM1M1, MM2MI, SK-Mel-28, and SK-Mel-37 to UV radiation were compared with those of normal human fibroblasts (NHF-2 and NHF-26), xeroderma pigmentosum cells (XP11MI), and HeLa S3 cells. Cell cultures were exposed to various doses of UV (254 nanometer, 1 Joule/square meter/sec) and cultured for 2 wk. Assays of colony-forming ability indicated that MM1MI cells were more resistant to UV than HeLa S3 and NHF-2 cells. Comparison of thymine dimer content showed no significant differences between MM1MI, SK-Mel-28, and HeLa cells, indicating that the resistance of MM cells was not the result of a lower level of UV damage. Measurement of excision repair by the 5-bromo-2'-deoxyuridine (BrdUrd) photolysis technique showed no differences between MM cells and other types. Measurement of unscheduled DNA synthesis labeling showed variations in incorporation of [3H]thymidine from cell to cell but no significant differences overall. Analysis of postreplication repair using [3H]thymidine and BrdUrd indicated that MM cells carried out de novo synthesis more rapidly than HeLa cells. The wt-av mol wt of newly synthesized DNA was reduced in the presence of caffeine, indicating that DNA repair in MM cells is caffeine-sensitive, and to a greater degree than other cell types. Resistance of MM cells to UV is apparently due to a caffeine-sensitive DNA repair mechanism. (26 Refs)

35. LYMPHOBLASTOID LINES AND SKIN FIBROBLASTS FROM PATIENTS WITH TUBEROUS SCLEROSIS ARE ABNORMALLY SENSITIVE TO IONIZING RADIATION AND TO A RADIOMIMETIC CHEMICAL.

Scudiero DA, Moshell AN, Scarpinato RG, Meyer SA, Clatterbuck BE, Tarone RE, Robbins JH
Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
J Invest Dermatol; 78(3):234-238 1982

Lymphoblastoid lines, derived by transforming peripheral blood lymphocytes with Epstein-Barr virus, and skin fibroblast lines were established from two patients with tuberous sclerosis. The number of viable lymphoblastoid cells was determined by their ability to exclude the vital dye trypan blue after their irradiation with x-rays or 254 nm ultraviolet light. The growth of fibroblasts was determined by their ability to form colonies after treatment with the radiomimetic, DNA-damaging chemical N-methyl-N'-nitro-N-nitrosoguanidine. The tuberous sclerosis lymphoblastoid lines were hypersensitive to x-rays but had normal sensitivity to the ultraviolet radiation. The tuberous sclerosis fibroblast lines were hypersensitive to the N-methyl-n'-nitro-N-nitrosoguanidine. The hypersensitivity of tuberous sclerosis cells to x-rays and to N-methyl-N'-nitro-N-nitrosoguanidine is believed to reflect defective repair of DNA damaged by these agents and may provide the basis for in vitro, including prenatal, diagnostic tests for tuberous sclerosis. (Author abstract) (51 Refs)

36. THE ACTIVITY OF INTERFERON ON ULTRAVIOLET LIGHT-INDUCED SQUAMOUS CELL CARCINOMAS IN MICE.

Bryak MM, Tschen EH, Hudson RD, Smith EB, Fleischmann WR, Black HS
Dept. Dermatology, Univ. Texas Medical Branch, Galveston, TX, 77550
J Am Acad Dermatol; 5(1):61-63 1981

Effects of virus type (VT: IF-alpha + IF-beta) and immune (I· IF-gamma) interferons (IF) used separately or in combination on epidermal tumors induced by UV light in albino hairless mice (SKH-Hv-1) were investigated. Mice were exposed to UV light (1.13 joules/square cm (cm2)/day initially to 1.97 joules/cm2/day through 16 wk). Eighteen tumors (squamous cell carcinomas) on nine mice were injected intralesionally with 3,000 units/site of VT-IF/day, 16 tumors on 9 animals received 10 units/site I-IF/day, 19 tumors on 9 mice received combined IF (3,000 units VT-IF and 10 units I-IF/site/day), and 19 control tumors on 10 mice received mock IF. No systemic effects of IF were observed. Results with I-IF were similar to those with mock IF. Tumor regression with VT-IF was greater than in controls, but the difference was not significant. Regression in the group receiving combined IF treatment was significantly greater than in controls. Thus, antitumor activity was enhanced by combining the two IF types, even though each IF was ineffective when used alone. (11 Refs)

37. INCREASED LEVELS OF 6-OXO-PGF1 ALPHA IN HUMAN SKIN FOLLOWING ULTRAVIOLET B IRRADIATION.

Black AK, Hensby CN, Greaves MW
Inst. Dermatology, Homerton Grove, London E9 6BX, England
Br J Clin Pharmacol; 13(3):351-354 1982

Skin levels of (prostaglandins: 6-oxo-PGF1 and 2 alpha, PGE2), following UV B irradiation, were measured. Levels of 6-oxo-PGF1 alpha, 6, 24, and 48 hr after irradiation were 43.0, 14.5, and 80 nanog/ml, respectively ; control levels were 8.7 nanog/ml. Concentrations of arachidonic acid, PGE2, and PGF2 alpha were elevated at 6 hr, reached a max at 24 hr, and returned to near control levels 48 hr following irradiation. UV B irradiation apparently activated the arachidonic acid metabolism causing increased concentrations of prostanoids. (12 Refs)

38. CULTURES OF BENIGN MELANOCYTIC NEVUS: PRELIMINARY INVESTIGATION.

Fimiani M, Mancianti ML, Fiori ML, Alessandrini C, Gerli R
Istituto di Clinica Dermosifilopatica, Universita di Siena, Siena, Italy
Boll Soc Ital Biol Sper; 57(18):1916-1920 1981

Cultures of benign melanocytic nevus (MN) were prepared from materials removed s urgically from five patients. The materials were histologically diagnosed and were cultivated according to the technique of Aubert. The cultivated cells were tested with hematoxylin-eosin (Giemsa) and with l-dihydroxyphenylalanine (DOPA) according to Becker; some were examined with the aid of electron microscopy according to a technique proposed by Keen. All the cultures of MN showed vigorous growth, and, after 48-72 hr, 70% of the transplants of the cultures were vital, having epithelial outgrowths more or less like complete crowns. After 5-7 days, 40-76% of the transplants showed cells with intensive proliferative growth (IPG) and elevated numbers of mitoses. Transplantation of these IPG cells produced monomorphous fibroblast-like cultures that reached saturation capacity within 15 days. These cells had relatively clear cytoplasms, small nuclei, and no specific markers. The DOPA reaction was intensely positive, especially in early growth phases. The study with the electron microscope showed the absence of desmosomes, keratohyalin granules, and filaments of keratin; however, the Golgi apparatus and the ergoplasm were well developed, and many mitochondria and vacuoles were observed. Numerous cytoplasmic bodies were present, with concentric lamellar structures similar to those of melanosomes. (7 Refs) (In ITA)

39. IN SITU DEMONSTRATION OF OKT 6-POSITIVE CELLS IN CUTANEOUS LYMPHOID INFILTRATES.

McMillan EM, Wasik R, Everett MA

Dept. Dermatology, Univ. Oklahoma, Health Sciences Center, Oklahoma City, OK

J Am Acad Dermatol; 5(3):274-279 1981

Tissue samples from patients with parapsoriasis (PS), discoid lupus erythematosis (DLE), actinic keratosis (AK), halo nevus (HN), or lichen planus (LP) were studied using the indirect immunoperoxidase technique and OKT 6, a monoclonal antibody directed against human common thymocytes. Types of PS included large-plaque atrophic (LPA), pityriasis lichenoides chronica (PLC), and lymphomatoid papulosis (LPL). OKT 6-positive cells were identified in dermal infiltrates in 4/6 cases of LPA-PS and 1/1 case of LPL-PS. In two cases of LPA-PS the positive cells accounted for 5-10% of the infiltrate cell population. Equivocal results were found in 2/6 cases of LPA-PS, 1/1 case of PLC-PS, 1/1 case of AK, and 1/1 case of PL. Negative results were found with infiltrates from 1/1 case of DLE and 1/1 case of HN. No conclusively positive results were obtained with non-PS conditions. Results obtained with cells fixed in paraformaldehyde were more variable than those with cells fixed in acetone, suggesting that acetone may be the better fixative for determining the presence of OKT 6 antigen. Results indicate that OKT 6-positive cells may be found outside the thymus in certain pathological conditions (LPA-PS and LPL-PS). Since conversion of both these conditions to malignant forms has been reported, presence of the OKT 6 antigen may be an indicator of risk of malignancy. The cells detected may be immature thymocytes or Langerhans cells. (17 Refs)

40. SEPARATION OF EPIDERMAL CELLS BY DENSITY CENTRIFUGATION: A NEW TECHNIQUE FOR STUDIES ON NORMAL AND PATHOLOGICAL DIFFERENTIATION.

Fischer SM, Nelson KD, Reiners JJ, Viaje A, Pelling JC, Slaga TJ

Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN, 37830

J Cutan Pathol; 9(1):43-49 1982

Murine keratinocytes, isolated by flotation trypsinization of skin, can be separated into five groups by centrifugation through Percoll, a colloidal silica gradient. Within each group a good correlation was found between density, plating efficiency, morphological appearance, DNA synthesis, and degree of keratinization/cornification. This method can be applied equally well to fetal, newborn, or adult keratinocytes and should be useful in a variety of studies including isolation of subpopulations of pathological cell types, work on chalones and hyperplastic diseases such as psoriasis, and in vitro transformation studies. (Author abstract) (17 Refs)

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Diagnosis, Treatment

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DIAGNOSIS

1. PROGNOSTIC FACTORS IN METASTATIC MALIGNANT MELANOMA. THE SOUTHEASTERN CANCER STUDY GROUP EXPERIENCE.

Presant CA, Bartolucci AA, Southeastern Cancer Study Group
1500 E. Duarte Road, Duarte, CA, 91010
Cancer; 49(10):2192-2196 1982

Two hundred seventy-seven evaluable patients with metastatic malignant melanoma without prior chemotherapy were entered into combination chemotherapy during trials in the Southeastern Cancer Study Group during the period between 1974-1978. In order to determine which prognostic factors were favorable for response to chemotherapy and for survival, an analysis was performed utilizing a logistic regression equation. Significant favorable prognostic variables for complete or partial tumor regression included no involvement of lung (p =

HE 20.3173/2:

0.045), no involvement of liver ($p = 0.08$), and possibly, receiving treatment schedule 361B of Table 1 ($p = 0.093$). It was notable that sex and initial performance status were not significant factors. Significant favorable prognostic variables for survival included high initial performance status (p less than 0.001), no involvement of liver ($p = 0.005$), sex-female ($p = 0.056$), and bone involvement only ($p = 0.057$); lack of brain involvement as a favorable factor was of only marginal statistical significance in this sample ($p = 0.1929$). Treatment protocol and treatment arm were not significantly associated with survival. These data indicate stratifications which could be considered in future therapeutic trials, and identify factors which may influence clinical decision making in palliative management of patients with metastatic malignant melanoma. (Author abstract) (11 Refs)

2. THE FEMALE SUPERIORITY IN SURVIVAL IN CLINICAL STAGE II CUTANEOUS MALIGNANT MELANOMA.

Shaw HM, McGovern VJ, Milton GW, Farago GA, McCarthy WH
Melanoma Clinic, Sydney Hosp., Macquarie St., Sydney, New South Wales, 2000, Australia
Cancer; 49(9):1941-1944 1982

Five-yr survival rates were similar in men and women with nodal metastases from malignant melanoma (clinical Stage II). This is in contrast to our previous studies on patients with localized disease (clinical Stage I) which indicated a marked female superiority in survival. To seek explanations for this, we examined in these patients with regional lymph node metastases, four factors which we previously showed to be of prognostic importance in patients with localized disease: (1) Age of patient: overall survival rate in Stage II women was markedly reduced due to an extremely poor prognosis for post-menopausal women; (2) Site of primary lesion: Stage II women had a preponderance of extremity lesions, but these were not more prognostically favorable anatomic locations than axial locations; (3) Tumor thickness: women with metastatic malignant melanoma had a significantly higher proportion of very thick lesions than men; and (4) Evidence of tumor regression: although men with very thin regressing tumors had a poor prognosis, there were too few lesions of this thickness in patients with Stage II melanoma to markedly influence overall survival. It was concluded that although overall 5-yr survival rates in men and women with clinical Stage II malignant melanoma were similar, if these patients were matched by age and thickness of primary lesion, a female superiority in survival did exist for young patients with very thick tumors. (Author abstract) (10 Refs)

3. POLYAMINE LEVELS IN BLOOD AND PLASMA OF PATIENTS WITH MALIGNANT MELANOMA.

Desser H, Klaring WJ, Luger T, Gebhart W
Ludwig-Boltzmann-Institut fur Leukamieforschung und Hamatologie, Hanusch-Krankenhaus, Heinrich-Collin-Strasse 30, A-1140 Wien, Austria
Onkologie; 5(1):36-37,40-41 1982

The polyamines putrescine, cadaverine, spermidine, spermine, and the amine histamine in whole blood and plasma of 42 patients with malignant melanoma were analyzed after cold acid extraction and ion-exchange chromatography by fluorescence detection. Depending on the degree of tumor spreading the patients were grouped into five subpopulations; results were statistically with the values obtained from a normal population. The mean values of polyamine concentrations in the patient groups were generally not distinguishable from the mean values of the controls. Solely the mean of the spermidine values of postoperative patients with or without medical therapy and the spermine mean value for postoperative patients in tumor Stage I and III were elevated. Cadaverine was never detected. The individual frequency of elevated polyamine levels in the plasma of single patients and variable, depending on patient subpopulation and polyamine under consideration. Spermidine was most frequently elevated (44%) in patients of tumor Stage I under immunotherapy. We conclude that due to the low frequency of polyamine elevations to be found in plasma of melanoma patients by our method no diagnostic or prognostic significance and only limited importance for monitoring patients under therapy can be claimed. (Author abstract) (29 Refs) (In GER)

4. AMELANOTIC MELANOMA - DEFINITIVE DIAGNOSIS WITH FLUORESCENCE (FALCK AND HILLARP METHOD).

Morishima T, Nagashima N, Hanawa S, Ishikawa T, Sato W
Dept. Dermatology, Nihon Univ. Sch. Medicine, Tokyo, Japan
Rinsho Hifuka; 35(8):705-710 1981

In amelanotic melanoma, it is not possible to use melanin production in diagnosing the melanoma. A case of amelanotic melanoma was diagnosed using the fluoroscopic method of Falck and Hillarp in a 73-yr-old man. The patient first noticed the lesion on his thumb 5 mo prior to the examination, and thought that it was a mild cigarette burn. Light microscopic examination of biopsy specimens with various stains showed no melanin granules in the tumor. Other histological features were consistent with malignant melanoma. The thumb was amputated. Presence of DOPA or DOPA-containing compounds enabled visualization of the melanoma cells as a yellowish green to green color with fluoroscopy. The level of 5-S-cysteinyldopa in urine was used as a biochemical marker of the presence of melanoma postoperatively. (8 Refs) (In JPN)

5. MALIGNANT MELANOMA WITH UNKNOWN PRIMARY SITE.

Lopez R, Holyoke ED, Moore RH, Karakousis CP
(c/o Karakousis), Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 19(3):151-154 1982

From 1955 to 1976, 129 patients were seen with metastatic malignant melanoma from an unknown primary site, comprising 8.1% of all the referred patients with malignant melanoma. Eighty-two percent of the patients presented with a history of mass or lump. Overall median survival and 5-yr survival rates after onset of symptoms were 10 mo and 13%, respectively. Patients with lesions of the head and neck area had 5-yr disease-free survival of 25%, whereas those with lymph node disease had a survival of 18%. Twenty-nine patients with regional disease had wide excision (usually lymphadenectomy) and their 5-yr disease-free survival was 58%. Regional disease with malignant melanoma of unknown primary site should be treated with radical surgical excision, since the survival is comparable or better to that of patients with regional disease having known and excised primary site. (Author abstract) (11 Refs)

6. IN SITU - DEMONSTRATION OF HELPER-T-LYMPHOCYTES IN CUTANEOUS MALIGNANT LYMPHOMAS BY DIAMINOPEPTIDASE IV (DAP IV).

Sterry W, Steigleder GK, Goos M, Meisterernst E
Universitat-Hautklinik, Joseph-Stelzmann-Strasse 5, D-5000 Koln 41, W. Germany
Z Hautkr; 57(8):567-570,573-576 1982

Sections of frozen material from lesions of patients without treatment were used for enzymes diaminopeptidase IV (DAP IV), unspecific acid esterase, and beta-glucuronidase determination. Helper-T-lymphocytes were demonstrated in tissue sections of cutaneous lymphoma by the DAP IV; the majority of DAP IV positive cells was found in plaque stage of mycosis fungoides, but DAP IV positive cells decreased considerably in malignant lymphomas. The DAP IV can be used for demonstration of normal and neoplastic helper-T-lymphocytes. (16 Refs) (In GER)

7. THE INFLUENCE OF LYMPH NODE METASTASIS AND ULCERATION OF PRIMARY MELANOMA ON GERMINAL CENTERS WITHIN DRAINING LYMPH NODES: A HISTOMORPHOMETRIC STUDY.

Weidner F, Schroll S, Schonberg A
Dept. Pathology, Loyola Univ. Medical Center, 2160 S. First Ave., Maywood, IL, 60153
Arch Dermatol Res; 272(1/2):155-161 1982

Occurrence, quantity, and area of germinal centers (GC) were studied in secondary folicles of lymph nodes (LN) draining the primary tumor, the metastatic tumor, or being directly affected with metastases. Sections of 722 LN from 72 patients with well-documented surface condition of the primary melanoma were available for Pathostage II study. As second group representing Pathostage I, 931 LN sections from 72 patients were selected for comparative investigation. In Pathostage I, 54.2% LN sections were associated with an ulcerated primary melanoma, and 67.0% demonstrated no GC. Correspondingly, 63.2% LN sections exhibited at least one GC, wherein the primary tumor was ulcerated. In Pathostage II, 48.2% LN sections were associated with an ulcerated primary melanoma, and 57.1% demonstrated no GC. In association with LN sections demonstrating at least one GC, the primary melanoma was ulcerated in 51.0%. In cases demonstrated GC the Pathostage II preparations were differentiated into LN which either were or were not directly affected by metastases. Of 1,653 sections, 1,036 did not show any GC. The remaining 617 sections contained 3,437 GC, av 5.57 GC/section. The number of GC/section ranged from 1-49. Only one or no GC were registered in 63% of LN dissected from patients without metastases, whereas more than nine GC were counted in 72.4% of Pathostage II LN. The optoelectric analysis of GC area performed on 617 LN sections revealed a total value of 143.14 mm2 for all GC examined. The av area was 0.232 mm2/LN section, and 0.041652 mm2/GC. The minimum av GC area of 0.8 mm2/LN section resulted from nodes draining nonulcerated, nonmetastatic primary tumors. (22 Refs)

8. THE RATIO OF GLYCOSAMINOGLYCANS TO COLLAGEN IN THE SKIN IN MALIGNANT MELANOMA.

Nissen HP, Kreysler HW
Dpet. Dermatology, Univ. Bonn, Venusberg, D-5300 Bonn 1, W. Germany
Arch Dermatol Res; 272(1/2):67-71 1982

Interactions of proteoglycans and collagen in the invasive zone of melanoma were studied in skin excisions obtained from 24 melanoma patients. The ratio of the sum of the glycosaminoglycans or proteoglycans to collagen is markedly increased in the center of the tumor compared to the marginal region. This might be attributable to a pathologic increase of the glycosaminoglycans or of the proteoglycans, or to the decrease of the collagen. (11 Refs)

9. ACRAL LENTIGINOUS MELANOMA.

Moulin G, Franc MP, Barrut D, Villeneuve A
Service de Dermatologie, Hopital de l'Antiquaille, F 69321 Lyon Cedex 1, France
Lyon Med; 247(3):75-81 1982

The authors report nine cases of acral lentiginous malignant melanoma. This type of melanoma occurs exclusively on palms, soles, nail bed and matrix. It is most commonly seen in females and in the 6th or 7th decade. A two-phase evolutive course is usually observed: first, a radially spreading growth presenting as an irregular pigmented spot, then a vertically invasive component. At this second phase, the prognosis is severe, between this of nodular malignant melanoma and that of spreading superficial malignant melanoma. The nodular component does not have any characteristic histopathological feature compared to other types of melanoma but the radially spreading component contains many melanocytes observed in the lower portion of hyperplasic epidermis. The pigmented melanocytic lesions occuring on elderly patients palms, soles or nails should be excised. (Author abstract) (13 Refs) (In FRE)

10. MORPHOLOGIC FEATURES OF TUMOR STAGE LESIONS OF MYCOSIS FUNGOIDES.

Carbone A, Volpe R, Laurent M, Di Filippo L
Departement d'Anatomie Pathologique, Istituto Scientifico per lo Studio e la Cura dei Tumori, V. le Benedetto XVo, 10, I-16132 Genova, Italy
Bull Cancer (Paris); 69(1):1-10 1982

A morphological analysis was carried out on a series of five patients, with tumor stage lesions of mycosis fungoides. The histological findings of skin, lymph nodes, spleen, liver and bone marrow were investigated. Histologically, the cutaneous infiltrate consisted of large cells (mycosis cells) and small atypical lymphoid cells (Lutzner cells). Among the large cells, which predominated in number, two principal types of cell could be distinguished: lymphoid cells comparable to the Lutzner cells because of their nuclear configuration, and poorly differentiated basophilic and pyroninophilic cells with irregular nucleus ('reticulum' cells?) or regular nucleus ('T-immunoblasts'?). Ultrastructural data of cutaneous lesion obtained for study from only one patient, were consistent with these findings. Lesions of lymph nodes and viscera consisted of a cellular composition which closely resembled that of cutaneous lesions. In particular, the large so-called mycosis cells were always found and represented a supportive histologic feature in identifying this disease. (Author abstract) (23 Refs) (In FRE)

11. IN SITU IDENTIFICATION OF LANGERHANS CELLS IN THE DERMAL INFILTRATE OF CUTANEOUS T CELL LYMPHOMA.

Chu A, Berger CL, Kung P, Edelson RL
(c/o Edelson) Dept. Dermatology, Coll. Physicians and Surgeons, Columbia Univ., 630 West 168th St., New York, NY, 10032
J Am Acad Dermatol; 6(3):350-354 1982

Skin biopsies from 28 patients with cutaneous T-cell lymphomas (CTCL, mycosis fungoides: 23/28), cutaneous metastases from B-cell lymphomas (BL: 2/28), or benign lymphocytoma cutis (BLC) were assayed using monoclonal antibodies reacting against Langerhans cells (LC) and cross-reacting with T- or B-lymphocytes, helper T-cells, or monocytes/histiocytes. None of the biopsied areas had been exposed to local or systemic treatment. In 22/23 CTCL biopsies, a minor (up to 5%) but significant proportion of the CTCL cells showed the LC surface phenotype, together with the phenotype of helper T-cells. No T-cell antigens were identified. Since the BL and BLC biopsies lacked cells having the LC surface phenotype, their presence of CTCL suggested that this neoplasm may be a T-cell neoplasm. (25 Refs)

12. THE MALIGNANT POTENTIAL OF SMALL CONGENITAL NEVOCELLULAR NEVI: AN ESTIMATE OF ASSOCIATION BASED ON A HISTOLOGIC STUDY OF 234 PRIMARY CUTANEOUS MELANOMAS.

Rhodes AR, Sober AJ, Day CL, Melski JW, Harrist TJ, Mihm MC, Fitzpatrick TB
Div. Dermatology, Hunnewell-3, Children's Hosp. Medical Center, 300 Longwood Ave., Boston, MA, 02115
J Am Acad Dermatol; 6(2):230-241 1982

Histologic features commonly associated with congenital nevi were sought in 234 primary cutaneous melanomas (119 males, 115 females, 12-90 yr old; mean, 48 yr old). Dermal nevocellular nevi (NCN) were identified in contiguity with 64/234 melanomas (27.4%). No giant congenital nevi were identified. Tumor-associated NCN with congenital features (NNCI) were identified in 19 patients (8.1% of the total group) and 'ordinary' or 'acquired' types of NCN (ON) in 45 patients (19.2% of the total group). Melanomas associated with NCN were significantly associated with primary sites on the torso, early age at diagnosis (up to 40 yr old), and superficial spreading melanoma (SSM) histologic type. Melanomas associated with NNCI were usually of SSM type (16/19 tumors); significantly larger numbers of melanoma-containing tissue specimens were available for review in this subgroup. The sex ratios in the patients with either type of NCN were comparable to the sex ration in the patients without NCN. NNCI was more often associated with melanoma arising from a pre-existing mole (57.9%) as compared to the ON type of NCN (42.2%) or the group without NCN (31.8%). In the NNCI group, 3/19 patients (15.8%) developed metastases and 2/3 patients died (10.5% of 19 patients). In the ON group, 26.7% developed metastases and 15.8% died. In the group without NCN, 35.3% developed metastases and 24.1% died. The results suggested that small congenital nevi may be precursors of at least some cutaneous melanomas (notably of SSN histology). The strength of the histologic association was highly dependent on the specificity of the methods used for detecting congenital nevi in the melanoma specimens. (33 Refs)

13. THE VALUE OF MALIGNANCY EVALUATION IN PATIENTS WITH DERMATOMYOSITIS.

Callen JP
Univ. Louisville Sch. Medicine, 323 East Chestnut St., Louisville, KY, 40202
J Am Acad Dermatol; 6(2):253-259 1982

Data on 57 patients with dermatomyositis (DM) and a total of 67 malignant tumors were studied, in an attempt to assess the usefulness of extensive malignancy evaluation (upper gastrointestinal series, barium enema, and iv pyelography) in DM patients. The identification of 26/67 cancers was obtained 2-264 mo before the diagnosis of DM (2-12 mo in 9/26 cases). The identification of 23/64 cancers was obtained 1-114 mo after the diagnosis of DM (2-12 mo in 11/23 cases). DM and 18/64 cancers were diagnosed simultaneously. Not directed malignancy searches did not identify any of the cancers. The tumors were discovered by history-taking (40/64 cancers), physical examination (14/64), or abnormal chest x-rays or laboratory findings (12/64). One tumor was discovered at autopsy. In greater than 90% of cases, the malignancies associated with DM (the commonest sites were the breast, lung, colon, and stomach) were not amenable to a 'routine malignancy search'. Several patients underwent an extensive 'malignancy search' without having had complete physical examinations. It is concluded that the routine use of extensive radiographic screening tests in DM patients is without value. Malignancy evaluations should be performed in DM patients with prior histories of cancer, unexplained symptoms, signs, or laboratory tests, and failure to respond to treatment. The relationship between DM and cancer in adults is not uniform by temporal, histological, or clinical criteria. Successful treatment of the tumor may lead to improvement or worsening of the DM. Recurrence of the cancer is not necessarily accompanied by a relapse of DM. (36 Refs)

14. DERMATOFIBROSARCOMA PROTUBERANS AND ITS TISSUE CULTURE STUDY - ULTRASTRUCTURAL, ENZYME HISTOCHEMICAL AND IMMUNOLOGICAL STUDY.

Yoshida H, Matsui K, Hashimoto K, Yumoto T, Mihara M
Dept. Pathology, Tottori Univ. Sch. Medicine, Nishi-Machi 86, Yonago, Tottori 683, Japan
Acta Pathol Jpn; 32(1):83-91 1982

Dermatofibrosarcoma protuberans arising in the thigh of a 23-yr-old female is reported with an investigation of tumor cell character by electron microscopy, enzyme histochemistry, immunological and in vitro tissue culture techniques. The tumor tissue showed histologically a peculiar storiform arrangement of plump spindle cells with dense proliferation. Electron microscope revealed histiocytic cell structures of some tumor cells; lysosomes, phagosomes, and sparse rough endoplasmic reticula. They revealed diffuse positive reactions to acid phosphatase (Ac Pase) and nonspecific esterase. Short-time culture of the tumor tissue indicated rather round and polygonal cells admixed with spindle cells, positive to Ac Pase and nonspecific esterase with diffuse reaction. Most of the round cells possessed Fc and C3 receptors on their surface and phagocytic activity. Dermatofibrosarcoma protuberans is probably a histiocytic tumor and structural characteristics of schwann cells were not recognized. (Author abstract) (12 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

15. ABSENCE OF MELANOMA SPECIFICITY IN THE REACTIVITY OF MELANOMA PATIENTS' SERA WITH CULTURED ALLOGENEIC MELANOMA CELL LINES.

Dent PB, Liao SK, McCulloch PB, Stone BR, Singal DP
Dept. Pediatrics, Ontario Cancer Treatment and Res. Foundation, Hamilton Clinic, Hamilton, Ontario, L8N 3Z5, Canada
Cancer; 49(10):2043-2048 1982

While patients with melanoma are known to produce antibodies against melanoma cells, the tumor specificity of these reactions has not been well documented. Using the sensitive mixed hemadsorption assay we have identified antibody against one or more of nine different cultured melanoma cell lines in only 9 of 48 patients with melanoma. Reactivity against melanoma cell lines was seen only in females, 9/27 vs 0/21 males. The strongest melanoma reactivity was seen in sera which also contained lymphocytotoxic antibody. The reactivity was not melanoma specific because it could be removed by absorption either with pooled platelets, nonmelanoma tumor cells or in two cases, by both. We conclude that the occurrence of specific antimelanoma antibodies against common or shared surface melanoma associated antigens is an uncommon event in melanoma patients not receiving specific active immunotherapy. The clinical significance of the observed reactivity and whether it is directed against cancer associated determinants, fetal antigens, or normal tissue or histocompatibility antigens requires further study. (Author abstract) (31 Refs)

16. CYTOTOXIC ANTIBODY REACTIVITY IN SERA OF MELANOMA PATIENTS AGAINST ALLOGENEIC AND AUTOLOGOUS CULTURED TUMOR CELLS AND FIBROBLASTS.

Brown JM, Shoffner PC, Tondreau SP, Matthews EJ, Terry WD, Rosenberg SA

Div. Surgical Oncology, Univ. Illinois Medical Center, 840 South Wood, Chicago, IL, 60612

Cancer Res; 42(6):2216-2222 1982

Using a complement-dependent microcytotoxicity assay, sera from melanoma patients were analyzed for antibody reactivity with cultured melanoma and normal adult skin fibroblasts. Sera from Stage I tumor-bearing patients prior to surgical excision, poor-prognosis Stage I and Stage II patients after tumor excision and lymphadenectomy but prior to adjuvant therapy, and normal individuals with a similar age and sex distribution were tested against a melanoma-fibroblast pair from an allogeneic donor. The groups displayed a wide range of cytotoxicity against both cell types, and no serum possessed melanoma-specific reactivity. Mean cytotoxicity of the Stage I tumor-bearing group was not significantly different (p greater than 0.05) from that of the normal group for either target cell, and patients whose tumors went on to recur were not different from nonrecurrent patients. The Stage I and II postlymphadenectomy patients were not different from the normals in fibroblast reactivity. However, melanoma reactivity was significantly higher in the postlymphadenectomy patients than the normals (p less than 0.02). This was the result of an elevated reactivity in the patient population who remained disease free compared to patients whose tumors went on to recur (p less than 0.01), although a large overlap existed between these two groups. Cytotoxicity against autologous melanoma and fibroblasts was observed with sera obtained throughout the clinical course of four Stage II patients, and no melanoma-specific reactivity was detected. Absorption with cultured fetal fibroblasts of sera from Stage II patients both before and after immunotherapy with Bacillus Calmette-Guerin and allogeneic melanoma removed reactivity against allogeneic and autologous melanoma and adult fibroblasts. Therefore, the predominant antibody reactivity detected in these patients was directed against common fetal fibroblast-associated antigen, and no evidence was obtained for the presence of antibodies reactive with unique or shared tumor-specific antigens. (Author abstract) (35 Refs)

17. SYSTEMIC ADMINISTRATION OF HUMAN LEUKOCYTE INTERFERON TO MELANOMA PATIENTS. I. EFFECTS ON NATURAL KILLER FUNCTION AND CELL POPULATIONS.

Golub SH, Dorey F, Hara D, Morton DL, Burk MW

Div. Oncology, Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024

JNCI; 68(5):703-710 1982

Natural killer (NK) cytotoxicty was assessed against K562 targets in 14 melanoma patients who received daily im doses of human leukocyte interferon (IFN) for 42 consecutive days. The most common pattern of NK activity was a decline from pretreatment levels 1 day after initiation of treatment, followed by increasing cytotoxicity with peak activity at Day 7 and a subsequent gradual decline to pretreatment levels during the remaining wk of treatment. This pattern was particularly apparent in patients who received 3 x 10(6) or 9 x 10(6) U IFN/day, while patients who received 1 x 10(6) U IFN/day tended to lack the decline at Day 1 and maintained the elevated NK activity past Day 7. Changes in NK activity could not be related to changes in absolute lymphocyte counts; to proportions of cells bearing membrane receptors for sheep RBC, of cells bearing membrane receptors for erythrocyte-antibody-complement, or of cells bearing FCgamma receptor, or to clinical response to IFN. (Author abstract) (23 Refs)

18. SYSTEMIC ADMINISTRATION OF HUMAN LEUKOCYTE INTERFERON TO MELANOMA PATIENTS. II. CELLULAR EVENTS ASSOCIATED WITH CHANGES IN NATURAL KILLER CYTOTOXICITY.

Golub SH, D'Amore P, Rainey M

Div. Oncology, Dept. Surgery, Univ. California Los Agneles Sch. Medicine, Los Angeles, CA, 90024

JNCI; 68(5):711-717 1982

Treatment of patients with malignant melanoma with daily doses of human leukocyte interferon (IFN) resulted in natural killer (NK) cytotoxicity that increased during the 1st week of treatment and subsequently declined to pretreatment levels despite continued IFN administration; events involved in these changes were examined. The increased cytotoxicity was associated with an increased number of cells able to bind K562 targets and an increased proportion of cells able to mediate cytolysis of K562 targets. The period of increasing NK activity was also associated with an increased ability to generate in vitro cytotoxic effectors against K562 targets by stimulation with allogeneic lymphoblastoid cells. The responding cells in this system were depleted of NK activity by adherence to immune complexes. These results suggested that increased NK activity during Week 1 of in vivo treatment was associated with augmentation of the development of NK cells from noncytotoxic precursors in addition to direct effects on NK cells. In contrast, the decline in NK activity appeared to be primarily a direct effect on NK cells, because these cells could no longer be augmented in vitro by additional IFN. The refractory state of IFN augmentation of cytotoxicity was limited to the period of IFN treatment in vivo, and responsiveness to IFN was promptly regained upon cessation of treatment. No evidence for the development of suppressor cells of NK effector function could be obtained. (Author abstract) (24 Refs)

19. FIVE MELANOMA-ASSOCIATED ANTIGENS IDENTIFIED BY MONOCLONAL ANTIBODIES.

Hellstrom KE, Hellstrom I, Brown JP, Yeh MY, Woodbury RG
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Protides Biol Fluid Proc Colloq; 29:877-882 1982

Mice were immunized with human melanomas and hybridomas were established that identify cell surface antigens. Five antigens were identified by monoclonal antibodies: antigens 3.1, p97, p155, p210, and 4.2. These antigens are described with respect to antibody, molecular nature, and specificity in cultured cells and biopsies. Antigen 3.1 is thought to be a glycolipid and exhibits specificity for a small subgroup of cultured melanomas and biopsy material from melanomas and normal tissues. Antigen p97 is a 97,000 mol wt glycoprotein with specificity for approx 50% of cultured melanomas and biopsy tissue from approx 50% of biopsied melanomas and some fetal tissues. Antigen p155 is a 155,000 mol wt protein (possibly a glycoprotein) and exhibits specificity in cultured and biopsied melanomas. Antigen p210 is a 210,000 mol wt protein (possibly a glycoprotein) exhibiting specificity in approx 30% of cultured melanomas and 25% cultures of other tumors and in biopsies of melanomas, other tumors, and adult and fetal brain. Antigen 4.2 may be a glycolipid and exhibits specificity for approx 80% of cultured melanomas and a few other tumors. The implications of these findings in diagnosis and therapy of human melanomas and other tumors are discussed. (24 Refs)

20. DIFFERENTIATION OF HUMAN T LYMPHOCYTES: II. PHENOTYPIC DIFFERENCE IN SKIN AND BLOOD MALIGNANT T-CELLS IN CUTANEOUS T-CELL LYMPHOMA.

Haynes BF, Hensley LL, Jegasothy BV
Dept. Medicine, Duke Univ. Medical Center, Box 3258, Durham, NC, 27710
J Invest Dermatol; 78(4):323-326 1982

The cell surface antigen phenotype of circulating and skin malignant T-cells in patients with cutaneous T-cell lymphoma were studied. The mature T-cell antigen phenotype of the malignant T-cells was identical for circulating and skin malignant T-cells. In contrast, skin malignant T-cells expressed the immature human T-cell antigen Thy-1, surface membrane transferrin receptors, and Ia-like determinants while circulating malignant T-cells did not express these antigens. Skin infiltrating T-cells in benign dermatoses also expressed Thy-1 and Ia-like determinants. These observations support the notion that the skin is a major site of extrathymic T-cell differentiation and may promote phenotypic changes in circulating T-cells that home to skin. (Author abstract) (24 Refs)

CHEMOTHERAPY

21. THE TREATMENT OF MYCOSIS FUNGOIDES WITH OINTMENT-BASED MECHLORETHAMINE.

Price NM, Deneau DG, Hoppe RT
Dept. Dermatology, Mycosis Fungoides Clinic, Stanford Univ. Medical Center, Stanford, CA, 94305
Arch Dermatol; 118(4):234-237 1982

The use of topical mechlorethamine hydrochloride in the treatment of skin disease has been restricted because of the frequent development of contact dermatitis. A series of 24 patients with mycosis fungoides in Stages 1A (8 patients), 1B (15 patients), and 2 (1 patient) were treated with ointment-based mechlorethamine, prepared by an anhydrous method. This preparation was therapeutically effective. Complete clearing occurred in 15 of 18 patients with active disease over evaluation periods of up to 27 mo, and one patient had partial clearing. Two patients showed a partial relapse during their evaluation periods. The incidence of contact dermatitis was very low: 8% in individuals with a history of hypersensitivity to mechlorethamine and 0% in patients being exposed to the medication for the first time. This new preparation has been shown to be effective therapy for mycosis fungoides. Patient use is associated with minimal side effects. (Author abstract) (18 Refs)

RADIOTHERAPY

22. CONVENTIONAL RADIOTHERAPY IN THE TREATMENT OF LENTIGO MALIGNA AND LENTIGO MALIGNA MELANOMA.

Harwood AR
Dept. Radiation Oncology, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, Canada
J Am Acad Dermatol; 6(3):310-316 1982

Conventional fractionated radiotherapy (RT) was given to 40 patients (12 men, 28 women, 30-96 yr old; 37/40 were greater than 60 yr old) with lentigo maligna (LM: 17/40) or lentigo maligna melanomas (LMM: 23/40), usually of the face (32/40). Local tumor control was complete in all patients. Two residual tumors and two local recurrences were successfully treated by surgery (3/4) or repeat RT (1/4). LM regressed completely within 3-15 mo (av, 7 mo); LMM regressed completely within 1-24 mo (av, 8 mo). No regional or distant recurrences developed. The duration of complete remission was 2-5 yr in 13/40 patients (6/13 with LM, 7/13 with LMM) and 7-13 yr in 2/40 (1/2 each with LM and LMM). The cosmetic results of RT were excellent. It is concluded that conventional fractionated RT is a simple and effective outpatient treatment for LM and LMM. (11 Refs)

CASE REPORTS

23. MALIGNANT MELANOMA AND DERMATOFIBROSARCOMA IN A 60-YEAR-OLD PATIENT WITH LIFELONG ACRODERMATITIS ENTEROPATHICA.

Shelley WB
Peoria Sch. Medicine, 123 S.W. Glendale Ave., P.O. Box 1649, Peoria, IL, 61656
J Am Acad Dermatol; 6(1):63-66 1982

A man with lifelong, familial acrodermatitis enteropathica (ADE) showed partial clearing of the skin disease with diiodohydroxyquinoline (was given when he was 35 yr old, continuing for several yr). He developed a dermatofibrosarcoma of the back in middle age (48 yr old) and an amelanotic melanoma of the ankle 11 yr later. Both tumors were successfully resected. After the melanoma was resected, zinc sulfate (Zn: 300 mg/day, po) was given, causing complete regression of the ADE for the first time in the patient's life. After 4 yr of Zn therapy, he showed no evidence of ADE or malignancy. It is suggested that the typical immunologic deficit of ADE may have promoted the development of the malignancies. Since ADE is now known to be a familial defect of Zn absorption, lifelong Zn supplementation may be an appropriate means of preventing the development of malignancy in patients with this rare disease. (18 Refs)

24. ACRAL LENTIGINOUS MELANOMA OF THE PENIS.

Jaeger N, Wirtler H, Tschubel K
Urologische Universitats-Klinik, Sigmund-Freud-Strasse 25, D-5300 Bonn-Verusberg, W. Germany
Eur Urol; 8(3):182-184 1982

The exceedingly rare occurrence of acral lentiginous melanoma is reported with reference to a case report. Thirty-four cases of a not further differentiated penis melanoma have been described so far in the literature. Partial amputation of the penis is the therapeutic method of choice if the stage is appropriate. The demand for resection of the melanomatous growth 3-5 cm into the healthy tissue is thereby met. Staging of the inguinal lymph nodes is necessary to establish the stage of the disease. (Author abstract) (6 Refs)

25. BASAL CELL TUMOR WITH ECCRINE DIFFERENTIATION (ECCRINE EPITHELIOMA).

Sanchez NP, Winkelmann RK
Section Publications, Mayo Clinic, Rochester, MN, 55905
J Am Acad Dermatol; 6(4,part1):514-518 1982

Two women (one 48 and another 58 yr old) presented with locally destructive but not metastasizing tumors of the scalp, invading the contiguous fat and perineural spaces. Both tumors had developed at the sites of lacerating injuries. The histologic features led to the diagnosis of basal cell carcinoma with eccrine differentiation (eccrine epithelioma). One patient developed one recurrence, 7 yr after tumor excision. The other patient developed multiple recurrences over a 12-yr period (a recurrence developing at 10 yr extended into the underlying bone) despite multiple excisions, and was eventually treated by chemosurgery and a skin graft. Eight other cases from the literature are discussed. (14 Refs)

26. BASAL CELL CARCINOMA IN SEBORRHEIC KERATOSIS.

Mikhail GR, Mehregan AH
Dept. Dermatology, Henry Ford Hosp., 2799 W. Grand Blvd., Detroit, MI, 48202
J Am Acad Dermatol; 6(4,part1):500-506 1982

A basal cell carcinoma (BCC) was identified in the central nodular area of a plaque of seborrheic keratosis (SK) in a 59-yr-old woman. The presenting complaints were increased pigmentation, crusting, and bleeding from the center of the plaque for 2 mo. A review of greater than 10,000 SK biopsies disclosed only 14 BCCs. The BCC was in direct contact with the epidermis of the SK in 11/14 patients and in the reticular dermis in 3/14. In one patient, the BCC was surrounded by SK of the hyperkeratotic, papillomatous type. Histologic examination of an SK plaque is indicated in the presence of bleeding inflammation, crusting, erosion, or ulceration. (10 Refs)

27. MYCOSIS FUNGOIDES PRESENTING AS AREAS OF HYPOPIGMENTATION: A REPORT OF THREE CASES.

Zackheim HS, Epstein EH, Grekin DA, McNutt NS
133 Arch St., Redwood City, CA, 94062
J Am Acad Dermatol; 6(3):340-345 1982

Foci of mycosis fungoides (MF) in dark-skined patients are usually hyperpigementated. In two black patients (a 22-yr-old woman and a 46-yr-old man) and a 75-yr-old Hispanic woman with patch-stage MF, most or all MF areas were hypopigmented. Total-body applications of nitroen mustard (HN2: 10 mg/day x 4 wk) caused 70% tumor regression in the oldest patient. She developed an enlarged lymph node after 3 mo of observation and was lost to follow-up 2 mo later. Total-body applications of carmustine (BCNU: 400-675 mg over 16-27 days) caused complete tumor regression in both black patients. The woman showed evidence of recurrent MF after 39 mo. The man developed a localized recurrence after 14 mo, which disappeared after 5 wk of topical BCNU (0.05% in ethanol) applications; he remained in remission 8 mo later. In all patients, the regressing MF foci and the normal skin became hyperpigmented. This reaction was transient in the normal skin. The MF foci developed about the same degree of pigmentation as the normal skin and remained in this stage during remission. In the man (whose mother and niece had lymphomas), MF was identified in biopsies of an erythematous plaque (present for about 8 yr) and a hypopigmented macular area of skin. This patient had been diagnosed as having vitiligo 16 yr previously, and had responded partially to intermittent methoxsalen-UV therapy. He said that areas of hypopigmented, macular skin had been present when the diagnosis of vitiligo was made (without a skin biopsy). This suggested that the 'vitiligo' may have represented an early stage of MF, although the late appearance of erythematous plaques argued against this possibility. These patients' paradoxical hyperpigmentation reactions to HN2 or BCNU suggested that MF foci contain some unidentified factor(s) that interfere with the pigmenting actions of these agents. (7 Refs)

28. SQUAMOUS CELL CARCINOMA IN DISSEMINATED SUPERFICIAL ACTINIC POROKERATOSIS.

Shrum JR, Cooper PH, Greer KE, Landes HB
(c/o Cooper) Dept. Pathology, Univ. Virginia Medical Center, Box 214, Charlottesville, VA, 22908
J Am Acad Dermatol; 6(1):58-62 1982

A 59-yr-old woman with a 24-yr history of disseminated superficial actinic porokeratosis (DSAP) of the extremities (a condition known to have involved four generations of her family) presented with a hyperkeratotic, verrucous plaque on the pretibial surface of one leg. The plaque was surrounded by DSAP foci. The patient showed no clinical or histologic evidence of actinic keratoses or Bowen's disease. The plaque was excised completely and identified asa squamous cell carcinoma, apparently arising from dysplastic epidermal cells located under the cornoid lamellae. The patient began using topical sunscreens after tumor resection, and showed no evidence of recurrence 9 mo later. (10 Refs)

29. FANCONI'S ANEMIA. TUMOR-LIKE WARTS, HYPERPIGMENTATION ASSOCIATED WITH DERANGED KERATINOCYTES, AND DEPRESSED CELL-MEDIATED IMMUNITY.

Johansson E, Niemi KM, Siimes M, Pyrhonen S
Dept. Dermatology, Helsinki Univ. Central Hosp., Helsinki, Finland
Arch Dermatol; 118(4):249-252 1982

A 27-yr-old man had had Fanconi's anemia (FA) for 20 yr. The patient had pancytopenia, retarded growth, hypogonadism, and chromosomal aberrations. He had freckle-like and darker pigmented macules scattered on his chest, shoulders, upper part of the back, and hips, with interspersed, hypopigmented areas. Biopsy specimens taken from both the hyperpigmented and hypopigmented spots showed a derangement of keratinocytes and nuclear abnormalities, more notable on sun-exposed skin sites. The patient also had numerous tumor-like, recalcitrant, viral warts. Immunologic studies showed normal humoral immunity, but there was evidence of depressed cell-mediated immunity. We speculate that the chromosomal aberrations, the depressed cell-mediated immunity, and the increased frequency of malignant neoplasms known to occur in patients with FA also reflect changes related to an increased susceptibility to viral infections. (Author abstract) (33 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

30. ORAL CONTRACEPTIVE USE AND MALIGNANT MELANOMA.

Bain C, Hennekens CH, Speizer FE, Rosner B, Willett W, Belanger C
(c/o Hennekens) Channing Lab., 180 Longwood Ave., Boston, MA, 02115
JNCI; 68(4):537-539 1982

There was no overall relationship between a prior history of oral contraceptive (OC) use and the development of melanoma among 141 cases of nonfatal malignant melanoma and 2,820 age-matched controls drawn from respondents to a large postal survey of registered US nurses; crude relative risk (RR) was 0.93 and 95% confidence limits (CL) were between 0.64 and 1.36. Adjustment for a number of additional variables did not alter this estimate materially. Duration of OC use and interval since first use were similarly unrelated to the occurrence of melanoma. For women diagnosed before age 40, there was a crude positive association of 'ever' use of OC and melanoma (RR = 1.78; 95% CL, 1.11-2.86). However, adjustment for geography and other variables diminished this association and rendered it statistically not significant (RR = 1.43; 95% CL, 0.83-2.46). These data do not support the hypothesis that OC use is an independent risk factor for melanoma. (Author abstract) (24 Refs)

31. OUTBREAK OF KAPOSI'S SARCOMA WITH CYTOMEGALOVIRUS INFECTION IN YOUNG HOMOSEXUAL MEN.

Urmacher C, Myskowski P, Ochoa M, Kris M, Safai B
Memorial Hosp., 1275 York Ave., New York, NY, 10021
Am J Med; 72(4):569-575 1982

Kaposi's sarcoma, a multicentric malignant neoplasm, occurs in certain geographic areas in the world. It is most common in Equatorial Africa and Eastern Europe. The annual incidence of Kaposi's sarcoma in the United States is between 0.021 and 0.061 per 100,000 persons. The appearance of an outbreak of Kaposi's sarcoma in young homosexual men in New York and California is a new and unique phenomenon. Certain differences are already recognized between the disease in these young men and the ordinary Kaposi's sarcoma. Herein we report our observations of the first 10 cases of Kaposi's sarcoma in young homosexual men. In these patients, the disease follows an aggressive clinical course characterized by widespread skin lesions with early involvement of the lymph nodes. In some of these patients, the result was death in a short period of time after initial diagnosis. In addition, cytomegalovirus infections were seen in these patients, which suggests at least a possible association between this virus and the disease. (Author abstract) (17 Refs)

32. MALIGNANT MELANOMA INCIDENCE AT THE LOS ALAMOS NATIONAL LABORATORY.

Acquavella JF, Tietjen GL, Wilkinson GS, Key CR, Voelz GL
J. F. A., Epidemiology Group, MS K-404, Health Div., Los Alamos Natl. Lab., Los Alamos, New Mexico, 87545
Lancet; 1(8277):883-884 1982

In an analysis of melanoma incidence for 1969 to 1978 among 11,308 workers at the Los Alamos National Laboratory in New Mexico 6 cases were detected in the total cohort, in which 5.69 cases would be expected (standardized incidence ratio [SIR] = 105; 90% confidence interval [CI] = 51,198) on the basis of incidence rates for the State of New Mexico, specific for age, sex, and ethnic origin. Among the white non-Hispanic men, three cases were detected, whereas 4.4 would be expected. The associated SIR of 68 (90% CI = 23,163) does not suggest excess melanoma incidence in this subcohort. A direct comparison with Statewide incidence rates gave similar results. These results do not agree with the threefold excess of malignant melanoma incidence found among white male employees at the Lawrence Livermore National Laboratory. (Author abstract) (10 Refs)

SELECTED PRECLINICAL STUDIES

33. ASSOCIATIONS OF PROPERDIN FACTOR B WITH MELANOMA.

Budowle B, Barger BO, Balch CM, Go RC, Roseman JM, Acton RT
Diabetes Res. and Training Center, Room 817, 1808 7th Ave. South, Birmingham, AL, 35294
Cancer Genet Cytogenet; 5(3):247-251 1982

We investigated 98 melanoma patients and 135 normal controls for differences in phenotype and genotype frequencies at the properdin factor B locus. A significant negative association with the Bf-F allele and melanoma was found, resulting in an estimated relative risk of 0.5. The estimated relative risk for developing melanoma among people with the Bf-FF genotype is 0.07. The Bf-S phenotype was significantly increased among the melanoma sample, with an estimated risk of 6.5. The data suggest association of the Bf locus with a melanoma protection and/or susceptibility gene(s). (Author abstract) (25 Refs)

34. EFFECT OF ADRENAL MANIPULATION ON GLUCOCORTICOID RECEPTORS IN MM1 HAMSTER MELANOMA.

Stanberry LR, Lindsey WF, Beattie CW
(c/o Beattie) Div. Surgical Oncology, Univ. Illinois Medical Center, 840 S. Wood St., Chicago, IL, 60612
Cancer Res; 42(6):2242-2246 1982

Cytosol glucocorticoid receptor of hamster Malignant Melanoma Number 1 (MM1) was characterized by dextran-coated charcoal and sucrose gradient assays. MM1 contains a specific, saturable, high-affinity (Kd 2.5 nM; 73.3 fmol/mg cytosol protein) receptor for glucocorticoid. The receptor sedimented at 7 to 8S in low-salt buffer and 5.5S in 0.4 M KCl and was sensitive to proteolysis by trypsin. Glucocorticoid receptor was inactivated by 40% $(NH_4)_2SO_4$. Addition of 20 nM molybdate to the homogenizing buffer prevented inactivation. Adrenalectomy increased MM1 receptor content without altering affinity. Chronic exposure of intact or adrenalectomized hamsters to gluco- and high-dose mineralocorticoid significantly decreased the amount of unbound glucocorticoid receptors available for binding. Exposure of intact hamsters to high doses of mineralocorticoid also decreased apparent receptor affinity. These results suggest that hamster MM1 contains a high-affinity cytosol receptor for glucocorticoids similar to that of other glucocorticoid-responsive tissues, which may mediate the action of adrenal steroids on tumor behavior. (Author abstract) (24 Refs)

35. A 94,000-DALTON GLYCOPROTEIN EXPRESSED BY HUMAN MELANOMA AND CARCINOMA CELLS.

Imai K, Wilson BS, Bigotti A, Natali PG, Ferrone S
(c/o Ferrone) Dept. Pathology and Surgery, Columbia Univ., 630 West 168th St., New York, NY, 10032
JNCI; 68(5):761-769 1982

The IgG2a monoclonal antibody (MoAb) 376.96S, secreted by a hybridoma derived from a mouse immunized with cultured human melanoma cells COLO 38, reacts with a single 94,000-dalton glycoprotein that is peripherally associated with the plasma cell membrane of cultured melanoma cells. Indirect immunofluorescence analysis with cryostat thin sections of human tissues showed that this antigen is absent from a large variety of normal tissues but is readily detectable on melanomas, nevi, and several different carcinomas. The MoAb376.96S binds with cultured melanoma and carcinoma cell lines to a similar extent and can mediate both complement-dependent and cell-dependent lysis of these cells. The 94,000-dalton glycoprotein detected by MoAb376.96S is distinct in its tissue distribution, antigenicity, and molecular profile from several structures previously identified with monoclonal antibodies that have similar molecular weights. (Author abstract) (24 Refs)

36. SELECTIVE PROLIFERATION OF NORMAL HUMAN MELANOCYTES IN VITRO IN THE PRESENCE OF PHORBOL ESTER AND CHOLERA TOXIN.

Eisinger M, Marko O
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Natl Acad Sci USA; 79(6,part1):2018-2022 1982

Cultures consisting almost entirely of human melanocytes were obtained from epidermal single-cell suspensions by using phorbol 12-myristate 13-acetate (10 ng/ml) in the culture medium. At this concentration, phorbol ester is toxic to human keratinocytes but not to melanocytes. When the seeding density was optimal (0.8-2 x 10(4)/cm2) and the medium contained both phorbol ester and cholera toxin, melanocytes proliferated extensively. Under these conditions, human melanocytes could be passaged serially in vitro and grown in quantity. This cell culture system can thus be used to answer basic questions related to pigment cell biology and may serve as a control for studies of malignant melanocytes. (Author abstract) (32 Refs)

37. PHASE I TRIALS OF MURINE MONOCLONAL ANTIBODIES TO TUMOR ASSOCIATED ANTIGENS: PRELIMINARY OBSERVATIONS.

Dillman RO, Sobol RE, Royston I
Dept. Medicine, Univ. California, San Diego, CA, 92161
Protides Biol Fluid Proc Colloq; 29:915-920 1982

Murine monoclonal antibodies (MoAbs) to tumor-associated antigens were infused into two patients with chronic lymphocytic leukemia (CLL) and two melanoma patients with advanced malignancies refractive to standard therapy. Prior to treatment, MoAb reactivity was confirmed in vitro with the patients' CLL cells or melanoma tissue. T101, an IgG2A produced by immunizations with T cell leukemia line 8402, was given to one CLL patient at doses of 1 and 3 mg on successive days then 12 mg 2 wk later, and a single 10 mg dose was given to the other CLL patient. Both melanoma patients were given single 10 mg infusions of M225, an IgGa2 produced by immunization with the M21 melanoma cell line. In circulating CLL cells, after infusion of T101, there was an immediate, marked decrease in lymphocyte number that reached a max in 2 hr, then rapidly increased. Serum MoAb had disappeared from circulation by 4 hr. Since T65 antigen persisted throughout the test period, no significant antigen modulation associated with leukemia cell recovery occurred. In melanoma patients, while no in vivo binding to tumor was demonstrated, M225 levels were still detectable 24 hr after infusion. Significant systemic reactions occurred with 10 and 12 mg infusions of T101; all resolved after administration of fluids and epinephrine. (17 Refs)

38. TISSUE DISTRIBUTION AND MOLECULAR PROFILE OF A DIFFERENTIATION ANTIGEN DETECTED BY A MONOCLONAL ANTIBODY (345.134S) PRODUCED AGAINST HUMAN MELANOMA CELLS.

Imai K, Natali PG, Kay NE, Wilson BS, Ferrone S
(c/o Ferrone) Dept. Pathology, Coll. Physicians and Surgeons, Columbia Univ., 630 West 168th St., New York, NY, 10032
Cancer Immunol Immunother; 12(2):159-166 1982

The mouse IgG2a monoclonal antibody (MoAb) 345.134S secreted by a hybridoma derived from a mouse immunized with cultured human melanoma cells was examined in relation to the structure of the target antigen, the distribution of the antigen in normal and malignant tissues, and the expression of the antigen on cultured cells and its ability to function as a target of immune lysis. The structure detected by the MoAb 345.134S is composed of an 85 kilodalton (KD) glycopolypeptide linked by disulfide bridges with a 30 KD polypeptide carrying little or no carbohydrate. The 115 KD antigen appears to be peripheral rather than integral to the plasma membrane. Indirect immunofluorescence studies showed that the reactivity pattern of normal tissues with MoAb 345.134S does not correlate with their embryological origin. The majority of normal tissues gave only weak staining with MoAb 345.134S. All the types of tumors tested, except liver adenocarcinomas, reacted strongly with MoAb 345.134S, although there were some cases within each tumor group that were negative. MoAb 345.134S reacted in a radioimmunometric assay with a variety of cell lines, including melanoma, carcinoma, and lymphoid types. There was no relationship between the level of expression of the antigenic determinant recognized by MoAb 345.134S and other surface markers tested. The level of antigen detected by MoAb 345.134S was unchanged in the presence of interferon but was decreased by puromycin exposure. The opposite was true for cell-dependent lysis of cultured human cells. (32 Refs)

39. INDUCTION AND TRANSPLANTATION OF MURINE SKIN CANCERS INDUCED BY METHOXSALEN PLUS ULTRAVIOLET (320-400 NM) RADIATION.

Kripke ML, Morison WL, Parrish JA
Cancer Biology Program, NCI-Frederick Cancer Res. Facility, P.O. Box B, Frederick, MD, 21701
JNCI; 68(4):685-690 1982

Properties of skin tumors resulting from treatment of mice with ip methoxsalen plus UVA (320-400 nm) radiation (PUVA) were compared to those of skin tumors induced by UVB (280-320 nm) radiation. Repeated treatment of C3H/HeN murine mammary tumor virus-negative (C3H-) mice with PUVA produced both fibrosarcomas and squamous carcinomas that were indistinguishable morphologically from UVB-induced tumors. Fragments of 12 primary PUVA-induced tumors were transplanted into normal and immunosuppressed syngeneic recipients, and all grew progressively. In contrast, 19 primary tumors induced by repeated exposure of C3H- mice to UVB grew only in the immunosuppressed mice and not in the normal recipients. The growth of graded doses of cells from 5 PUVA-induced tumors was compared in normal and UVB-irradiated recipients. No preferential growth in UVB-irradiated mice was observed, even though this is characteristic of UVB-induced tumors. Thus PUVA-induced tumors do not appear to have the same antigenic properties as UVB-induced tumors. (Author abstract) (22 Refs)

40. ALTERED EPIDERMAL GROWTH FACTOR (EGF)-STIMULATED PROTEIN KINASE ACTIVITY IN VARIANT A431 CELLS WITH ALTERED GROWTH RESPONSES TO EGF.

Buss JE, Kudlow JE, Lazar CS, Gill GN
(c/o Gill) Dept. Medicine, Div. Endocrinology, Univ. California San Diego Sch. Medicine, La Jolla, CA, 92093
Proc Natl Acad Sci USA; 79(8,part1):2574-2578 1982

To determine the role of epidermal growth factor (EGF)-stimulated protein kinase in the biological effects caused by EGF, tyrosine-specific kinase activity has been quantitated in A431 human epidermoid carcinoma cells and six variant cell lines. Because EGF inhibited proliferation of A431 cells, variants resistant to this inhibition were selected by treatment with mutagen and maintenance for 1 month in 0.1 uM EGF. After cloning and growth for 6-20 generations without EGF, the resistance of the variants to the growth-inhibitory effect of EGF was confirmed. Whereas EGF increased cellular phosphotyrosine content approx 10-fold in parental A431 cells, EGF caused smaller or undetectable increases in the six variant cell lines. Solubilized membranes from the six variants displayed diminished EGF-stimulated phosphorylation of the EGF receptor and of antibodies to p60src (the product of the Rous sarcoma virus transforming gene), which act as an exogenous substrate. The decrease in EGF-stimulated tyrosine-specific protein kinase activity varied from approx 40% (Clone 16) to approx 8% (Clone 18) of parental A431 activity. Phosphorylated EGF receptors from parental and variant cells migrated identically on sodium dodecyl sulfate/polyacrylamide gels. The number of EGF receptors in variant cells decreased in parallel with EGF-stimulated protein kinase activity, so that the specific activity of EGF-stimulated protein kinase per EGF receptor remained constant in the six variant cell lines with reductions in both activities to as low as 10%. These results suggest that this tyrosine-specific protein kinase activity mediates the growth-inhibitory effect of EGF on A431 cells and that both EGF binding and kinase activities reside in the same or tightly associated molecules. (Author abstract) (30 Refs)

41. RESISTANCE TO PHOSPHATASE OF THIOPHOSPHORYLATED EPIDERMAL GROWTH FACTOR RECEPTOR IN A431 MEMBRANES.

Cassel D, Glaser L.
Dept. Biological Chemistry, Div. Biology and Biomedical Sciences, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
Proc Natl Acad Sci USA; 79(7):2231-2235 1982

Epidermal growth factor (EGF) increases the phosphorylation of its receptor and other membrane proteins, and these proteins can be rapidly dephosphorylated by membrane-bound protein phosphatase. We report that [35S]adenosine 5'-[gamma-thio]triphosphate is as effective as [gamma-32P]ATP as substrate for the EGF receptor-associated protein kinase in A431 membranes. Both the kinetics and the extent of the EGF-dependent thiophosphorylation at 0 C are similar to those obtained with [gamma-32P]ATP, provided that ATP hydrolysis by the membrane preparation is inhibited by addition of adenosine 5'-[beta,gamma-imino]triphosphate. The thiophosphorylation reaction requires Mn++ but differs from the phosphorylation reaction in the inability of Mg++ to serve as cofactor. Both EGF-dependent phosphorylated and thiophosphorylated membrane proteins yield the same two major bands of Mr 145,000-160,000 in autoradiograms of Na-DodSO4/polyacrylamide gel electrophorograms. The rate of dephosphorylation of membrane proteins that have been thiophosphorylated in the presence of EGF is dramatically slower (factors of 1/20 to 1/40) than that of the phosphorylted proteins at both 0 C and 32 C. This increased metabolic stability of the thiophosphorylated proteins will be useful for investigation of the role of phosphorylation in the biological effects of EGF. (Author abstract) (22 Refs)

42. EPIDERMAL GROWTH FACTOR INHIBITS GROWTH OF A431 HUMAN EPIDERMOID CARCINOMA IN SERUM-FREE CELL CULTURE.

Barnes DW
Dept. Biological Sciences, Univ. Pittsburgh, Pittsburgh, PA, 15260
J Cell Biol; 93(1):1-4 1982

A medium consisting of a rich basal nutrient mixture supplemented with bovine insulin (10 ug/ml), human transferrin (10 ug/ml), human cold-insoluble globulin (5 ug/ml), and ethanolamine (0.5 mM) supported the growth of the A431 human epidermoid cell line in the absence of serum with a generation time equal to that of cells in serum-containing medium. Addition of epidermal growth factor (EGF) to this culture medium at concentrations mitogenic for other cell types resulted in a marked inhibition of A431 cell growth. Inhibitory effects of EGF were observed at 1 ng/ml and near-maximal effects were observed at 10 ng/ml. The inhibitory effect of EGF could be reversed by the omission of EGF in subsequent medium changes and could be prevented by the addition of anti-EGF antibody to the culture medium. Inhibition of A431 cell growth by EGF also could be demonstrated in serum-containing medium. (Author abstract) (34 Refs)

43. ORNITHINE DECARBOXYLASE ACTIVITY IN CHEMICALLY INDUCED MOUSE SKIN PAPILLOMAS.

Astrup EG, Boutwell RK
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Carcinogenesis; 3(3):303-308 1982

The activity levels of L-ornithine carboxy-lyase (ODC) (EC 4.1.1.17) and S-adenosyl-L-methionine carboxy-lyase (SAM-D) (EC 4.1.1.50) were determined in individual papillomas induced in mouse skin by a two-stage technique, and in normal mouse epidermis. Cycloheximide treatment abolished both enzyme activities. In normal epidermis the ODC activity was barely detectable, whereas the tumors exhibited high levels of ODC. Levels of SAM-D activity above those of normal epidermis were detected in some papillomas, but in contrast to ODC the SAM-D activity levels were not consistently increased in skin tumors. By pooling a great number of papillomas, the variations in ODC and SAM-D activities between different papillomas could be minimized so that reliable measurements of the biological half-lives of ODC and SAM-D in the tumors were obtained using cycloheximide treatment. The half-life of SAM-D in squamous papillomas was 45 min, almost identical to the 41 min half-life of the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced level of this enzyme in normal mouse epidermis. In contrast, the ODC activity of the mouse skin papillomas declined at a rate similar to that in TPA-treated epidermis for only the first 15-20 min after cycloheximide injection. Thereafter, at time points when protein synthesis was approx 90% inhibited, the ODC activity reverted to high levels. These results show that the high level of ODC activity in squamous papillomas is stabilized. This observation is compatible with the hypothesis that the control mechanism of the ODC activity level in these tumors is severely deranged. This change in polyamine turnover pattern may be related to altered differentiation of the epidermal cells, which constitute the main bulk of cells in these tumors. (Author abstract) (40 Refs)

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DIAGNOSIS

1. CLINICAL-PATHOLOGIC-GENETIC NUANCES IN THE FAMMM SYNDROME (MEETING ABSTRACT)

Lynch HT, Fusaro RM, Pester J, Albano WA, Kimberling WJ, Lynch JF, Scheulke GS, Haynes WA, Recaben JA
Creighton University School of Medicine, Omaha, NE, 68178
Proc Am Soc Clin Oncol; 1:C-1 1982

We describe the salient clinical-pathologic-genetic features of four kindred with the Familial Atypical Multiple Mole Melanoma syndrome (FAMMM). Intra- and inter-family differences are examined. Certain patients with extraordinary clinical phenomenon are presented: viz, a) bilateral intraocular melanoma, in context with multiple cutaneous malignant melanoma (CMMs); b) a 28 year old female nondrinker-nonsmoker with squamous cell carcinoma of the oral cavity and synchronous CMM; c) a patient with 9 CMMs whose sister had 4 CMMs; d) examples of variable gene penetrance wherein two obligate gene carriers in a family, one of whom survived to age 75, failed to express phenotype; e) extracutaneous cancers occurring in excess among direct line relatives of these kindreds; and f) apparent long term survival from CMM(s). Segregation analysis on the families was done. Probands and all direct line an-

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centers were excluded in order to avoid ascertainment bias. The segregation ratio was 0.43, a significantly less than 0.5, indicating a rate of nonpenetrance of 0.14. The rate of penetrance was slightly dependent on age. Atypical moles and malignant melanoma were the most reliable clinical signs of being affected. Extracutaneous cancer was associated. Clinical-pathological-genetic variation must be scrutinized in FAMMM kindreds so that maximum advantage can be given to potential diagnostic-etiologic clues. The FAMMM gene shows pleiotropic effects, predisposing to cancer of multiple anatomic sites. (no Refs)

2. 'MICROSCOPIC SATELLITES' ARE HIGHLY PREDICTIVE OF LYMPH NODE METASTASES IN CLINICAL STAGE I MELANOMA (MEETING ABSTRACT)

Harrist TJ, Rigel D, Day CL, Sober AJ, Lew RA, Harris MN, Kopf AW, Fitzpatrick TB, Mihm MC
Departments of Pathology and Dermatology, Massachusetts General Hospital, Boston, MA
Lab Invest; 46(1):35A 1982

In a multivariate analysis of 19 clinicopathologic variables from 327 prospectively studied melanoma patients who underwent elective regional lymph node dissection (ERLD), we selected primary tumor thickness, 'microscopic satellites', and the elapsed interval between diagnosis and ERLD as the best predictive model of clinically occult nodal metastases. The probability of finding nodal metastases for melanomas less than 0.75 mm thick was 0 per cent; for those 0.76 to 1.50 mm, 4 per cent; 1.51 to 3.0 mm, 14 per cent; and less than 3.0 mm, 39.5 per cent (30 of 76). Primary melanomas greater than 1.50 mm thick with microscopic satellites were more often associated with nodal metastases than those of similar thickness without satellites. Microscopic satellites are defined as tumor nests, greater than 0.05 mm in diameter, that reside in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor mass but separated from it by normal tissue on the section in which the Breslow measurement was taken. A subset of these satellites probably represent intraspecimen metastases, wherea others do not. The 5-year survival rate for clinical stage I patients with satellites was 36 per cent in contrast to 89 per cent for those without them. More nodal metastases were found when ERLD was delayed greater than 50 days after biopsy. (no Refs)

3. PROGNOSTIC PARAMETERS AND TREATMENT OF RECURRENT MELANOMA (MEETING ABSTRACT)

Karakousis CP, Temple DF, Moore R
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Soc Clin Oncol; 1:C-270 1982

Prognostic correlations were sought in recurrent melanoma. In 361 patients with recurrent melanoma the clinical stage was the strongest determinant of subsequent survival; 160 patients with regional node metastases (IIIB) had 5 year survival 24.4%; 63 with prior disease free interval (FI) from excision of the primary less than 1 year had median survival (MS) 15.8 months (MO) with 10 (16%) disease free (DF) at 5 years, while 89 patients with FI greater than or equal to year had MS 23.7 MO with 27 (30%) DF at 5 years. In stage IV, 51 patients with FI less than 2 years had MS 5.4 MO, while 69 patients with FI greater than or equal to 2 years had MS 10.4 MO; 52 patients with 1 metastatic nodule initially had MS 10 MO while 69 patients with greater than or equal to 2 nodules had MS 6.9 MO. Age, sex and anatomical site of the primary had no influence on survival after recurrence. In a prospective study from 6/77 through 6/80, 79 consecutive patients with recurrent melanoma had excision of all gross tumor and various adjuvant protocols. Of 7 patients stage IIIA, 5 remain DF at 25.5 MO. Of 33 patients with advanced stage IIIB (fixed nodes, in 16 involving two node groups) 10 patients (30%) remain DF at 30 MO; all 10 DF patients had less than or equal to 3 lesions, while 11 with progression had less than or equal to 3 nodules and MS 18 MO and 12 had greater than 3 nodules and MS 10.5 MO. Among the 23 failed 14 with FI greater than or equal to 12 MO had MS 17.2 MO while 9 with FI less than 12 MO had MS 10.9 MO. Of 12 patients stage IIIAB, 11 with greater than 3 lesions died, and 1 with 3 lesions is DF at 26 MO. Of 27 patients stage IV 8 (30%) remain DF with MS 36 MO. (no Refs)

4. DYSPLASTIC NEVI IN HISTOLOGIC ASSOCIATION WITH 234 CUTANEOUS MELANOMAS (MEETING ABSTRACT)

Rhodes AR, Harrist TJ, Mihm MC, Day CL, Sober AJ
Departments of Dermatology and Pathology, Harvard Medical School, Boston, MA
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Dysplastic nevi (DN) have been clinically associated with both familial and sporadic melanoma. The characteristic histologic feature of DN include epidermal hyperplasia, intraepidermal atypical melanocytic hyperplasia (distinguishable from melanoma in situ), a frequently associated dermal nevocellular nevus (NCN), and one or more dermal mesenchymal changes. To further assess a role for DN in the evolution of cutaneous melanoma, we searched for the characteristic intraepidermal features of DN immediately adjacent to 234 melanomas of all histologic types, invasive to at least Clark's level II. Nine of these 234 cases were histologically interpreted as lentigo maligna melanoma, excluded from further analysis. Of the remaining 225 cases, 49 had associated intraepidermal features of DN. Of these 49 cases, 22 were associated with a dermal NCN, compared with 42 of 176 non-DN cases. Of these 22 NCN, eight had at least one feature more commonly noted in congenital than acquired NCN. The 49 DN cases were significantly less often associated with nodular melanoma than the 176 non-DN cases. (no Refs)

5. N-ACETYLNEURAMINIC ACID (NANA) AND PROGNOSIS IN MALIGNANT MELANOMA (MM) (MEETING ABSTRACT)

Silver HK, Murray RN, Karim KA, Salinas FA, Spinelli JJ
Cancer Control Agency of British Columbia, Vancouver, British Columbia V5Z 3J3, Canada
Proc Am Soc Clin Oncol; 1:C-7 1982

We have previously shown that serum NANA concentration can serve as a relatively sensitive monitor of tumor burden in a variety of neoplasms including MM. In this study we wished to determine the relationship of serum NANA to known prognostic factors for MM. Eligible MM patients (pts) had no evidence of residual disease at the time of serum sampling, have been followed for 2-5 yrs, and include 151 pts, with initial disease confined to the primary site (stage I) and 10 pts with regional lymphatic extension (stage II). A Cox proportional hazards model was used to identify significant independent predictors of disease free survival (DFI). Four of the 9 factors examined were not predictive: sex, primary site, tumor diameter, and stage. Satisfactory analysis of stage was precluded by the small stage II group. Five factors were significant predictors: measured depth of primary invasion, p equals 7x10(-7); anatomic depth, p equals 7x10(-6); NANA, p equals 0.003; age, p equals 0.005; and growth pattern (superficial spreading vs nodular) p equals 0.01. Only 2 of these predictors were independent; Measured depth and NANA. NANA may prove useful in identifying high risk MM pts, especially those with measured depth greater than 1.5 mm. (2 Refs)

6. A STATISTICAL STUDY OF 56 PATIENTS TO DETERMINE THE PROGNOSIS OF MALIGNANT MELANOMAS OF THE CONJUNCTIVA AND EYELIDS.

Haye C, Saragoussi J, Asselian B, Schlienger P, Calle R
Section Medicale et Hospitaliere, Institut Curie, 26, rue d'Ulm, 75231 Paris, France
J Fr Ophtalmol; 5(3):159-166 1982

The long-term prognosis of malignant melanoma of the conjunctiva and eyelids was analyzed in 56 patients (20 men and 36 women, av age 57.5 yr). The following results were obtained: 85.6% of the patients were alive 5 yr, 68.2% were alive 10 yr, and 54.9% were alive between 15 and 20 yr. Mortality increased progressively over time and then remained stable after 12 yr. When compared with other cancers, the prognosis seemed relatively good at 5 yr but at 15 yr nearly half of the patients had died because of their disease. Sex and patient age did not affect the survival rate. Survival at 5 yr was 91.7% for those patients whose initial treatment was surgery and 77.3% for those patients who received radiotherapy. Survival at 20 yr was 55.2% for surgery patients and 45.9% for radiotherapy patients. In 80% of the patients (36/56) there was local or nodal recurrences. No recurrence were seen for 48.3% patients still alive at 5 yr, for 31.7% at 10 yr, and for 21.1% at 15 and 20 yr. The survival rates following recurrence were 49% at 5 yr, 31.5% at 10 yr, and 26.2% at 15 and 20 yr. Patients treated with combined surgery and radiotherapy had the best prognosis and patients treated with radiotherapy alone had the worst prognosis. (19 Refs) (In FRE)

7. CLINICAL AND LABORATORY FEATURES OF KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN (MEETING ABSTRACT)

Kris M, Safai B, Myskowski P, Kozner B, Urmacher C, Gold J, Armstrong D, Pinsky C, Krown S, Ochoa M, Sherlock P
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Am Soc Clin Oncol; 1:C-700 1982

A cluster of Kaposi's Sarcoma (KS) cases has been observed among young homosexual men in the New York City area. Ten patients (pts), all with the onset of symptoms after 12/78, have been seen. THe median age was 38 years (range 32-55); 9 were white and 1 was an American black. Initial sites of disease were skin (8) and oral mucosa (2). Lymphadenopathy was seen in 7 pts and hepatosplenomegaly in 1 on initial examination. One pt had Pneumocystis carinii pneumonia at diagnosis. Gastrointestinal involvement was documented in 5 of 7 pts completely evaluated by either endoscopy or necropsy. Cytomegalovirus (CMV) titers were greater than 1:32 in 9 pts; 1 was anticomplementary. One pt had a 4-fold rise in CMV titer during his illness. Epstein-Barr viral capsid antigen titers, measured by the immunofluorescent antibody technique, were greater than 1:160 in 9 pts tested. CMV was cultured from the urine of 2 of 7 pts. Oral cultures grew Candida albicans in 3 pts. Antibody to hepatitis B was noted in all 5 tested pts. Serum immunoglobulins G, A, and M were normal or elevated in all 6 pts tested. Significantly lower ratios of T-helper (OKT4+) to T-suppressor (OKT8+) cells were noted in KS pts when compared to normal controls using anti-T-cell monoclonal antibodies. Two of the 10 pts died 10 and 16 months after histologic diagnosis despite treatment with chemotherapy. No other pts have received chemotherapy to date. (no Refs)

8. CARCINOMA CUNICULATUM (VERRUCOUS CARCINOMA OF THE SKIN). A CLINICOPATHOLOGIC STUDY OF 46 CASES WITH ULTRASTRUCTURAL OBSERVATIONS.

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Cancer; 49(11):2395-2403 1982

Forty-six examples of carcinoma cuniculatum, a rare variant of squamous cell carcinoma of the skin, were studied by means of light and electron microscopy and immunoperoxidase techniques. The tumors usually presented as ulcerated, fungating, and polypoid masses with openings of sinus tracts onto the skin surface that exuded foul-smelling greasy material when pressure was applied. On microscopic examination the tumors were seen to be composed mainly of mature squamous keratinocytes with foci of cellular atypia. Electron microscopic studies revealed features of well-differentiated squamous cell carcinoma. The tumor may affect any cutaneous area of the- the body, and there is a predilection for the feet, particularly the soles. The cause must still be determined, but trauma, chronic irritation, and/or viral infection may play a role. The neoplasm is a low-grade carcinoma capable of local invasion, extension into bone, and rare metastasis to the regional lymph node. Although immunoperoxidase studies revealed no inclusions, infection by human papilloma virus (HPV) remains a possibility (Author abstract) (24 Refs)

9. ADENOID BASAL CELL CARCINOMA OF THE VULVA (MEETING ABSTRACT)

Merino MJ, LiVolsi VA, Schwartz PE, Rudnicki J

Departments of Pathology and Gynecology, Yale University, New Haven, CT

Lab Invest; 46(1):56A 1982

Vulvar carcinomas are rare, accounting for less than 4 per cent of all female pelvic cancers. Of this, squamous cell carcinomas are the most commonly found. Basal cell carcinomas are tumors that frequently occur in the sun-exposed areas of the skin. In the vulva however, they are unusual. The biologic behavior of vulvar basal cell carcinoma has been debated with some series suggesting they are very low grade lesions and others reporting aggressive behavior. We had the opportunity to study two cases of a specific subtype, the adenoid basal cell type. Both patients were 84 years old and had the tumor mass present for several years. Much confusion exists in regard to this entity. Because of their histologic appearance consisting of strands of epithelial cells forming tubular and gland-like structures whose lumina may be filled with mucoid substances, they are frequently misdiagnosed as adenoid cystic carcinomas. The specific form of presentation and pathologic findings warrant their differentiation from: (1) adenoid cystic carcinomas, tumors usually associated with an aggressive and infiltrative behavior and (2) ordinary basal cell carcinoma occurring on vulvar skin. (no Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

10. AN ANALYSIS OF SKIN TESTS AND THEIR RELATIONSHIP TO RECURRENCE AND SURVIVAL IN STAGE III AND STAGE IV MELANOMA PATIENTS.

Lee ET, Ishmael DR, Bottomley RH, Murray JL

Dept. Biostatistics and Epidemiology, Univ. Oklahoma Health Sciences Center, P. O. Box 26901, Oklahoma City, OK, 73190

Cancer; 49(11):2336-2341 1982

One-hundred-two patients with Stage III and IV malignant melanoma were analyzed to determine whether immunologic status in terms of skin testing along with sex and age played a role in recurrence and survival. Before treatment, patients had skin tests with five recall antigens (monilia, mumps, PPD, SK-SD, trichophyton) along with phytohemagglutinin (PHA). Univariate statistical analysis revealed sex as the major significant variable with respect to survival for Stage IVB patients, with female patients surviving longer than males. Patients with resected disease and greater SK-SD skin test reactivity tended to survive longer than those with impaired reactivity. Similarly, reactivity to trichophyton was associated with improved survival among patients with metastases. A multivariate analysis of the patients shows improved remission duration with mumps positivity in Stage III and Stage IVA patients. It appears that certain skin tests analyzed in this fashion have prognostic importance in these patients and should be analyzed with other variables of disease status. (Author abstract) (16 Refs)

11. EVALUATION OF ASSAYS TO DETECT IMMUNE COMPLEXES AS AN IMMUNODIAGNOSTIC AID IN PATIENTS WITH MELANOMA.

Ruell P, Murray E, McCarthy WH, Hersey P

Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, Australia

Oncodev Biol Med; 3(1):1-12 1982

Sera from 211 melanoma patients were tested before and after surgery for the presence of immune complexes (ic) by the 125I-C1q radioimmunoassay (C1q RIA) and a nephelometric monoclonal rheumatoid factor assay (mRhF). The patients were grouped according to stage of disease and therapy. Before surgery Stage III patients had a higher incidence of ic (26.9%) than Stage II (17.5%) and Stage I (6.1%) patients. The incidence of ic in the latter patients did not differ from that of normal controls. Stage I patients treated with BCG therapy had a higher incidence of ic before and after surgery to remove melanoma compared with untreated patients. The incidence of ic in Stage I and II patients was higher in sera taken after surgical removal of tumor compared to that in sera taken before surgery. Sequential studies revealed that ic often appeared then disappeared prior to clinical detection of recurrences. These results suggested that antigen excess was a frequent cause for failure to detect ic A prospective evaluation of the usefulness of assays for ic to monitor disease activity in melanoma patients was conducted. In some individual patients detection of ic was a prelude to recurrence from melanoma but the high false negative rate and the presence of elevated ic levels unrelated to recurrent tumor suggested that these assays should be of limited diagnostic value in the management of melanoma. (Author abstract) (23 Refs)

12. DETECTION OF A HUMAN MELANOMA-ASSOCIATED ANTIGEN, P97, IN HISTOLOGICAL SECTIONS OF PRIMARY HUMAN MELANOMAS.

Garrigues HJ, Tilgen W, Hellstrom I, Franke W, Hellstrom KE

Program in Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104

Int J Cancer; 29(5):511-515 1982

The unlabeled antibody technique of Sternberger was used to study the localization in histological sections of human melanoma-associated antigen p97, which is defined by a monoclonal antibody. The antigen was detected in 8 of 10 primary skin melanomas, in 6 of 7 metastatic melanomas and in 2 of 2 compound nevi. It was localized at the cell surface, the cytoplasm and the nucleus always being negative. The antigen was not seen in cells from three basal cell carcinomas, one squamous cell carcinoma, one leiomyosarcoma, or in samples of normal skin (including keratinocytes, connective tissue consisting of collagenous and elastic fibers, fibroblasts, sebaceous glands, blood vessels, smooth muscles, or inflammatory cells such as granulocytes, lymphocytes and macrophages), kidney or lung. There was, however, staining of some cells in the secretory segment of eccrine sweat glands from two patients, possibly corresponding to myoepithelial cells. Antigen expression was somewhat variable between cells from different melanomas as well as between individual cells from the same melanoma. The possible diagnostic value of this procedure for identification and classification of melanomas is discussed. (Author abstract) (24 Refs)

13. ISOLATION OF TUMOR-ASSOCIATED ANTIGEN (TAA) FROM SERUM OF MELANOMA PATIENTS (MEETING ABSTRACT)

Leitch AM, Gupta RK, Morton DL

Surgical Oncology, University of California Los Angeles School of, Medicine Los Angeles, CA, 90024

Proc Am Soc Clin Oncol; 1:C-164 1982

We have been investigating the effect of extracorporeal immunoadsorption (ECIA) in patients with advanced melanoma. Though the exact mechanism of this treatment is unknown, the removal of blocking immune complexes might be one among several. This investigation was undertaken to determine if the immunoadsorption column could remove TAA from the serum of melanoma patients. The plasma of melanoma patients was circulated over a column packed with heat-killed, formalin-fixed Staphylococcus aureus Cowan I. After treatment, S aureus was removed from the columns, washed with Phosphate-buffered saline (PBS) and eluted with glycine-HCl (pH 2.8) buffer. The eluate was filtered through a membrane with 50K dalton exclusion limits. The material retained on the filter was tested in the radioimmunoassay (RIA) and the enzyme-linked immunosorbent assay (EIA) for the presence of two different TAAs described previously. The processed eluate (200 ul) from two melanoma patients showed 100% inhibition in RIA at high protein concentrations (5 mg/ml) but no inhibition at low concentrations (0.05 mg/ml). In competitive EIA the extent of inhibition was 40-60% by the two eluates (50 ul each) at high protein concentrations. Control samples comprised of blood-bank plasma treated S aureus and eluted as above showed less than 10% inhibition in RIA and less than 20% inhibition in EIA at 6 mg protein/ml. These results suggest that ECIA could be used to isolate TAA from plasma of cancer patients. (no Refs)

14. LOCALIZATION OF RADIOLABELED MONOCLONAL ANTIBODIES IN HUMAN MELANOMA AND CARCINOMA XENOGRAFTS IN NUDE MICE (MEETING ABSTRACT)

Mann BD, Saxton RE, Cohen MB, Spolter L, Benedict WF, Storm FK, Morton DL
University of California at Los Angeles School of Medicine, Los Angeles, CA, 90024
Proc Am Assoc Cancer Res; 23:1041 1982

We have isolated two monoclonal antibodies which react strongly with tumor cells but not with lymphoid cell lines from melanoma and carcinoma patients. One antibody, 436G10 (IgG1 isotype), binds to 13/17 melanoma cell lines, but to only 2/10 carcinoma cell lines by the indirect 125I protein A assay. The second antibody, 44X14 (IgG1 isotype), binds to 8/8 carcinomas and 0/6 melanomas. Paired label experiments were performed in nude mice to see if the unique and divergent in vitro binding patterns of these antibodies occurred in vivo. Nude mice bearing a melanoma or carcinoma or both were injected IV with 5-8 ug of each monoclonal antibody labeled with 25-50 uCi of either 125I or 131I; in separate animals the labels were reversed. Animals were sacrificed 4 days following injection. Binding advantages of the monoclonal antibodies were computed by the following equation: Binding advantage equals Tumor/tissue ratio specific monoclonal/Tumor/tissue ratio nonspecific monoclonal. Antibody 436 had up to a two-fold binding advantage for melanomas, whereas antibody 44 had up to a two-fold advantage for carcinomas. In animals having both melanomas and carcinomas, the binding advantages were consistent for each histologic type. Though these results confirmed the in vitro specificities, binding advantages were modest, suggesting a high degree of nonspecific binding. (no Refs)

15. ANTITUMOR ACTIVITY OF INTERFERON: IN VITRO STUDIES ON HUMAN MELANOMA (MEETING ABSTRACT)

Fisher PB, Kellogg C, Sheffield K, Graham GM, Grant S, Pestka S, Oster MW, Weinstein IB
Cancer Center/Institute of Cancer Research, Columbia University, New York, NY, 10032
Proc Am Assoc Cancer Res; 23:898 1982

In the present study we have used a human melanoma cell line (HO-1) to evaluate the ability of both crude KG-1 (crude-IF) and bacterial-cloned (IF1rA) human leukocyte interferon (IF) to inhibit the in vitro growth of tumor cells in agar suspension. We found that both types of IF caused a 50% inhibition in cloning efficiency of this cell line in agar (LD50) at concentrations in the range of 125-175 units/ml. The cloning efficiency was reduced greater than 80% by 1000 IF units/ml with HO-1 cells not previously exposed to IF, and also with HO-1 cells that were grown as monolayer cultures for one week in the presence of 1000 units/ml of IF1rA prior to plating in agar. A series of colonies that survived growth in agar in the absence or presence of 500-1000 units/ml of either crude IF or IF1rA were isolated from the agar plates and then maintained in monolayer culture in the absence of IF. When these clones were reseeded into agar 5 subcultures later, these clones displayed a 9-29 fold greater cloning efficiency than the parental cell line. When rechallenged for growth in agar in the presence of 1000 units IF1rA/ml, the clones that had not been previously exposed to IF exhibited a 74+/-12% inhibition in cloning efficiency, whereas the clones that had been previously exposed to IF displayed only a 51+/-7% reduction in cloning efficiency. The selection of variants of melanoma cells that have increased resistance to growth inhibition by IF may explain the limited success of this agent in the treatment of human melanoma. (no Refs)

16. THE CELL POPULATION IN THE CUTANEOUS INFILTRATE OF MYCOSIS FUNGOIDES: IN SITU STUDIES USING MONOCLONAL ANTISERA.

Holden CA, Morgan EW, MacDonald DM
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Br J Dermatol; 106(4):385-391 1982

T cell antigens were studied in cutaneous sections from five patients with mycosis fungoides (MF). The method allowed cell counting to be undertaken for each monoclonal antiserum. OKT3 (pan T cell) antiserum confirmed the predominantly T lymphocytic nature of the infiltrate, labeling the majority of infiltrating cells. OKT4 (helper/inducer) antiserum positively labeled 90% of the lymphocytes identified as OKT3+. OKT8 (suppressor) antiserum marked only single or small groups of dermal lymphocytes, which comprised 24% of the cells identified as T lymphocytes. OKT6 (anti-Langerhans) showed positive labeling of dendritic cells in the epidermis and dermis. Fewer positively labeled epidermal dendritic cells were observed in sections from patients receiving PUVA, but no difference was found in the number of OKT6 positive dermal cells. The ratio of helper to suppressor cells in the dermal infiltrate significantly exceeded the normal circulating ratio. (Author abstract) (16 Refs)

17. IN SITU IMMUNOLOGIC PHENOTYPING OF MYCOSIS FUNGOIDES.

McMillan EM, Wasik R, Beeman K, Everett MA
Dept. Dermatology, Univ. Oklahoma Health Science Center, Oklahoma City, OK
J Am Acad Dermatol; 6(5):888-897 1982

In situ analysis of mycosis fungoides (MF) infiltrates with the use of monoclonal antibodies directed against T cells and T cell subsets in conjunction with the indirect immunoperoxidase technique is described. Punch biopsies were taken from six patients with MF. Two patients were affected by tumor stage MF and the remainder by plaque stage. The specificity and source of antibodies used are presented. In one patient with MF plaque stage, weak reactivity was observed with peripheral T cell antibodies, Leu 1, and OKT 3, in approx 50% of the cells. In three patients with plaque stage MF and one with tumor stage MF, a significant component of the dermal infiltrates (greater than or equal to 50%) was found to react positively with peripheral T cell antibodies Leu 1 and OKT 3. The results in the dermis with 'helper' antibodies Leu 3A and OKT 4 also indicated that a significant component of the populations reacted positively with these antibodies. Testing of the dermal infiltrates with 'suppressor' antibodies Leu 2 and OKT 8 gave a negative reaction in one patient and a positive reaction in a small number of cells in three patients. The majority of cells in the Pautrier abscesses stained positively with the peripheral T cell antibodies. Analysis with 'helper' antibodies gave a positive reaction in many of the cells constituting the abscesses. Testing with the 'suppressor' antibodies gave a negative reaction in the Pautrier abscesses in all three patients. Results in the positive control of tonsil were positive with all primary antibodies, with a predominantly interfollicular distribution of positive-reacting cells. Results with Leu 1 and OKT 3 indicate that a significant component of cutaneous infiltrating mononuclear cells of MF react with antibodies which normally detect mature T cell antigens. (33 Refs)

CHEMOTHERAPY

18. TREATMENT OF METASTATIC MALIGNANT MELANOMA WITH A TWO-PART CHEMOTHERAPY REGIMEN CONSISTING OF VELBAN-BLEOMYCIN-CISPLATIN (V-B-P) FOLLOWED BY DTIC-DIBROMODULCITOL (DTIC-DBD) (MEETING ABSTRACT)

Richman S, Woodcock TM, Blumenreich MS, Kubota TT, Bland K, Moore C, Allegra JC
Department of Medicine, University of Louisville School of Medicine, Louisville, KY, 40292
Proc Am Soc Clin Oncol; 1:C-665 1982

Patients with recurrent disseminated malignant melanoma were treated with two courses of monthly Velban 6mg/M2 day 1 and 2, Bleomycin 15u/M2 daily as a continuous infusion day 1-5, and cisplatin 50 mg/M2 day 5 to further evaluate reports of high activity with this regimen. Because this regimen exhausted the acceptable Bleomycin dose, a second regimen was instituted regardless of response to that point consisting of dacarbazine (DTIC) 800 mg/M2 day 1 and DBD 125 mg/M2 day 1-10 (every 28 days). Fifteen patients have been entered thus far. All but 1 (adjuvant Semustine) were previously untreated with systemic chemotherapy. Fourteen are evaluable for toxicity and response. Five were treated with only one course of V-B-P because of gross disease progression. Three of these 5 went on to receive DTIC-DBD; two did not respond and one is too early. Of the 14 evaluable patients, there were 4 partial responses (PR), 1 pulmonary, 2 subcutaneous, and 1 mediastinal. Duration of response was short. Responses did not continue after switching to DTIC-DBD. All four responders failed with CNS metastates. Median survival for the 14 patients was 5 months, for responders 7.5 months, for nonresponders 3 months. Toxicity consisted of nausea-vomiting (100%), stomatitis (36%), and myelo-suppression. Two patients developed life threatening infections related to myelosuppression. No patient was, in fact, treated with 2 full courses of the V-B-P regimen. Reductions in the Velban dose from 33%-50% were made in every case. Thus the overall response rate thus far is 4/14 (28%, PR only). (1 Ref)

19. CHEMOIMMUNOTHERAPY IN DISSEMINATED MELANOMA: A SOUTHWEST ONCOLOGY GROUP STUDY (MEETING ABSTRACT)

Costanzi JJ, Al-Sarraf M, Frank J
University of Texas Medical Branch, Galveston, TX, 77550
Proc Am Soc Clin Oncol; 1:C-655 1982

This study was a prospective randomized study in patients with disseminated malignant melanoma who were tested with either carmustine (BCNU), Hydroxurea, and dacarbazine (DTIC) (BHD) or BHD plus Levamisole (CT+IT) or high dose DTIC plus Actinomycin D (DIC-DAC). A number of patient factors were examined and the randomization did achieve a balance between treatment arms. Two hundred and twenty-one patients were treated and responses were noted in 14/49 on BHD (29%), 24/84 (29%) for CT+IT, and 21/88 (24%) for DIC-DAC. Previous extensive experience with BHD noted a response rate of 30%. When all patients were considered there was no statistical difference in survival but of those who responded the BHD responders had a median survival of 28 weeks, CT+IT-20 weeks and DIC-DAC 47 weeks. Certain factors were statistically significant in determining longer survival. These included female sex, better performance status, absence of brain, liver, or bone involvement, hemoglobin greater than 11.0, and lymphocyte counts greater than 2000 per dl. Toxicity was acceptable with the majority of the patients experiencing mild to moderate nausea, vomiting, and leukopenia. One patient had life threatening leukopenia which was reversible. (no Refs)

20. HYPERTHERMIC REGIONAL PERFUSION WITH MELPHALAN AND A COMBINATION OF MELPHALAN AND ACTINOMYCIN D IN THE TREATMENT OF LOCALLY METASTASIZED MALIGNANT MELANOMAS OF THE EXTREMITIES.

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J Surg Oncol; 20(1):9-13 1982

From September 1969 through 1979, 68 patients with already locally metastasized malignant melanomas of the extremities were treated by hyperthermic regional perfusion and local excision(s). Of these, 53, patients could be evaluated after a follow-up of at least 2 yr: 31 had been perfused with melphalan and 22 with melphalan in combination with actinomycin D. Local recurrence rates were about the same in both groups: 32 versus 33%. The same applied to the symptom-free interval between perfusion and local recurrence: about 12 versus about 13 mo. Virtually all recurrences in both groups (90 versus 85%) were seen within 2 yr. The interval between perfusion and systemic metastization was also roughly the same; about 25 versus about 23 mo. These results indicate the need for better chemotherapeutics in order to achieve further improvement. The results of these perfusions were otherwise by no means disappointing, and hyperthermic regional perfusion is indicated in the treatment of patients with locally metastasized malignant melanomas. (Author abstract) (20 Refs)

21. A PHASE II STUDY OF DIBROMODULCITOL (DBD) IN STAGE IV MELANOMA (MEETING ABSTRACT)

Hopkins J, Richards F, Case D, Pope E, Spurr C, White D, Jackson D, Stuart J, Muss H, Cooper MR
Bowman Gray School of Medicine, Winston-Salem, NC, 27103
Proc Am Soc Clin Oncol; 1:C-696 1982

During the period 11/78-8/81, 24 patients were evaluated in a non-randomized study to assess the effectiveness of DBD in Stage IV melanoma. Patients received 100 mg/m2 of DBD orally for 35 nights. The dose was then escalated to 130 mg/m2 nightly for the next 35 days, and then to 160 mg/m2 nightly, if no significant hematologic toxicity occurred. There were no objective responses, including 6 patients who had had no prior chemotherapy. Five patients (21%) remained stable (defined as less than 50% change in the lesions for a minimum of 8 weeks with no appearance of new lesions). Median survival was 151 days (range 10 to 543+ days). Survival favored females, non-visceral involvement pre-therapy, and patients with a disease free interval (DFI) of greater than 1 year. None of these advantages was statistically significant using the Gehan-Wilcox test for differences in survival distributions, however. Toxicity was predominantly hematologic, with 13 patients experiencing hemoglobins less than 10 gm, 5 patients with WBC less than 3,000/mm3 and 4 patients with platelet count less than 50,000/mm3. Other reported toxicities include nausea, vomiting, shortness of breath, and diarrhea, but none occurred in greater than 15% of the patients. Oral DBD, using this dose and schedule, does not appear efficacious in the treatment of patients with advanced disseminated melanoma. (no Refs)

22. PRELIMINARY RESULTS OF BOLD FOR DISSEMINATED MELANOMA (MEETING ABSTRACT)

Ahn SS, Morton DL
Division of Surgical Oncology, University of California at Los Angeles, School of Medicine, Los Angeles, CA, 90024
Proc Am Soc Clin Oncol; 1:C-697 1982

Thirty-one patients with measurable disseminated malignant melanoma were treated with Bleomycin, Oncovin, Lomustine, and DTIC (dacarbazine) (BOLD) during 1980-1981. This chemotherapy regimen, includes Bleomycin (B) 7.5 units subcutaneously in the first course and 15 units in subsequent courses on Days 1 and 4, Vincristine or Oncovin (O) at 1 mg/m2 intravenously on Days 1 and 5, CCNU or Lomustine (L) at 80 mg/m2 po on Day 1, and DTIC (D) 200 mg/m2 intravenously on Days 1-5. To date, 23 patients have received two or more courses of BOLD and have been followed long enough to evaluate their clinical response. Two patients (9%) demonstrated complete tumor regression and 7 (30%) had partial regression of greater than or equal to 50% of tumor mass and no new lesions. Four patients (17%) had stabilization of their disease, defined as no measurable growth and no new lesions. Ten patients (43%) failed to respond and showed progression of their disease. Presently, follow-up is too short to analyze the response duration and survival. Toxicity was mild to moderate, and there was no chemotherapy-related death. We conclude that BOLD is an effective treatment for disseminated melanoma and is superior to previously described chemotherapy. (1 Ref)

23. ACTINOMYCIN-D PLUS 5-(3,3-DIMETHYL-1-TRIAZENO)-IMIDAZOLE-4-CARBOXAMINE (DTIC) WITH OR WITHOUT INTRAVENOUS CORYNEBACTERIUM PARVUM IN METASTATIC MALIGNANT MELANOMA.

Robidoux A, Getterman JU, Bodey GP, Hersh EM
(c/o Hersh) Dept. Developmental Therapeutics, M.D. Anderson Hosp., Houston, TX, 77030
Cancer; 49(11):2246-2251 1982

Chemotherapy and chemoimmunotherapy of Stage IV B malignant melanoma were compared in 88 patients. Chemotherapy consisted of 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) 250 mg/M2 of the body surface area daily x 5 days and actinomycin-D 2 mg/M2 on day 1 repeated every 3-4 wk. Chemoimmunotherapy consisted of the same regimen plus corynebacterium parvum 2 mg/M2 iv daily for 14 days before every third cycle of chemotherapy, plus 2 mg/M2 iv daily on days 7 and 14 of each 21-28 day chemotherapy cycle. There was 32 evaluable chemotherapy and 33 evaluable chemoimmunotherapy patients and the groups were well balanced for clinical and pathologic as well as prognostic variables. The complete and partial remission rates, remission and survival durations, and hematologic and gastrointestinal toxicities were different in the two randomized groups being 6 and 3%, 9 and 9%, 7.6 and 12 mo, 8.8 and 6.0 mo, 20 and 16%, and 62 and 70%, respectively for these parameters. This difference was not statistically significant. Therefore, it can be concluded that the results of chemotherapy with actinomycin-D plus DTIC were not substantially different from those reported using DTIC alone, and that we cannot recommend the addition of actinomycin-D to DTIC for palliative management in these patients. Furthermore, C parvum immunotherapy did not add to chemotherapy in terms of remission rate, remission duration, or survival for patients with Stage IV B malignant melanoma. (Author abstract) (17 Refs)

24. HYPERTHERMIC ISOLATION PERFUSION WITH IMIDAZOLE CARBOXAMIDE IN DEEPLY INVASIVE AND RECURRENT MALIGNANT MELANOMA (MEETING ABSTRACT)

Didolkar MS, Elias EG, Pfefferkorn R
University of Maryland Hospital, Baltimore, MD
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

In the past 15 years, incidence of local recurrence, intransit metastases and lymph node metastases after wide surgical excision has been reported as 10-20%, 12-20% and 50% respectively. Most of the recurrences occurred in the first 18 months. This figure is much higher in melanomas which are greater than 1.5mm thick by Breslow's microstaging. Ten patients with Clark's level III, IV and V and Breslow's 1.5 to 4.5mm depth were treated by wide excision, skin grafting and hyperthermic isolation perfusion chemotherapy with DTIC (Imidazole Carboxamide). Median depth of invasion was 2.6mm. Dose of DTIC used was 2 gm/M2. Average core temperature of extremity was raised up to 39C. Perfusion done at the time of wide excision in 4 patients and within 10 weeks in 6 patients. None of the patients had regional lymph node dissections done except in two where the lesions were in upper extremity and axillary lymph node dissection was performed for better access to axillary vessels. Follow-up period ranges from 4+ months to 21+ months with median period of 15+ months. None of the patients have shown any evidence of local, regional or lymph node metastases. Low WBC and platelet count was noted in one patient and deep vein thrombosis in another patient. High dose DTIC was used because of higher response as compared to other systemic chemotherapeutic agents. Additionally, when it was used with perfusion in 5 patients with locally recurrent melanoma, all of these showed complete response so far for a median follow-up period of 19+ months. (no Refs)

25. PHASE II TRIAL OF VP-16213 IN DISSEMINATED KAPOSI'S SARCOMA (KS) (MEETING ABSTRACT)

Laubenstein L, Hymes K, Krigel R
New York University Cancer Center, New York, NY, 10016
Proc Am Soc Clin Oncol; 1:C-680 1982

An outbreak of disseminated KS has recently been described in homosexual men. This tumor has displayed a rapidly progressive course with involvement of skin, lymph nodes, gastrointestinal tract, and lungs. Preliminary data has suggested a role for combination chemotherapy consisting of Adriamycin (A), bleomycin (B) and vinblastine (V). Our clinical experience has indicated that there may be a less aggressive form of disseminated KS and that initial combination chemotherapy might not be appropriate for this entity. Single agent chemotherapy with VP-16213 was chosen as first line treatment for patients with apparently indolent disease because of its limited toxicity, broad anti-tumor activity and absence of cross resistance with agents in the ABV regimen. Ten patients with disseminated KS were treated with 27 courses of VP-16213 at a dose of 150 mg/m(2)/d x 3 d, q 4 weeks. Five patients had only skin or nodal disease; five had visceral disease in addition to skin and nodal involvement. Two patients achieved CR (complete response); four PR (partial resonse), two NR (no respose), and two too early to evaluate. Toxicity consisted of leukopenia and alopecia in all patients; stomatitis and parotitis each complicated one course. No infectious complications occurred in association with leukopenia. Both treatment failures have achieved PR's with ABV treatment. (no Refs)

RADIOTHERAPY

26. ELECTRON BEAM THERAPY FOR DIFFICULT CUTANEOUS BASAL AND SQUAMOUS CELL CARCINOMA.

Miller RA, Spittle MF
Dalhousie Univ., Halifax, Nova Scotia
Br J Dermatol; 106(4):429-435 1982

Electron beam therapy was used to treat 29 patients with squamous or basal cell carcinomas considered unsuitable for surgery or conventional superficial x-ray therapy. Primary control failed in two patients at 2 and 5 yr. Good cosmetic and functional results occurred in all patients treated. The advantages of this therapy in the management of cutaneous tumors which are difficult to treat are discussed. (Author abstract) (10 Refs)

MUTLIMODAL THERAPY

27. REDUCED INCIDENCE OF LOCO-REGIONAL RECURRENCES IN MELANOMA USING BCG IMMUNOTHERAPY AFTER SURGERY (MEETING ABSTRACT)

Paterson AH, Willans D, Jerry LM, McPherson TA
Cross Cancer Institute, Edmonton, Alberta, Canada
Proc Am Soc Clin Oncol; 1:C-662 1982

A prospectively controlled, randomized clinical trial was carried out to determine whether a combination of local perilesional intradermal (ID) and systemic oral BCG immunotherapy given after surgery to patients with Stage 1 melanoma would reduce the overall recurrence rate and improve survival. Patients with Stage 1 melanoma, Clarke's level (CL) 3-5 were eligible for trial entry, and after surgical wide excision and consent, were randomly allocated to either routine follow-up or adjuvant BCG immunotherapy. Immunotherapy consisted of ID BCG 40 mgs by Heaf Gun around the site of local surgery followed by oral BCG 40 mgs for 5 days each month for one year. ID BCG was then repeated at the same time and oral BCG was continued for one further year. One hundred and seventy-one patients have been entered into the trial, 83 in the treatment group and 88 in the control group. Side-effects and toxicity have been minimal. There have so far been 40 recurrences: 15 in the treatment group and 25 in the control group. Twenty-six patients have died: 10 in the treatment group and 16 in the control group. Using this form of immunotherapy, there has been a modest reduction in the incidence of local and regional recurrence as site of first recurrence but not of distant metastases. The overall recurrence rates show a trend in favor of the BCG group, which is not statistically significant. (no Refs)

CASE REPORTS

28. DISSEMINATED INFECTION DUE TO MYCOBACTERIUM AVIUM-INTRACELLULARE IN A HOMOSEXUAL MAN WITH KAPOSI'S SARCOMA.

Fainstein V, Bolivar R, Mavligit G, Rios A, Luna M
Dept. Developmental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
J Infect Dis; 145(4):586 1982

A case of Kaposi's sarcoma of the skin and scalp that did not respond to antibacterial or anticancer drug therapy is described. The 36-yr-old patient had pneumonia due to Pneumocystis carinii combined with elevated cytomegalovirus (CMV) titer; disseminated mycobacterial infection was another manifestation of severe immunodeficiency. CMV may trigger immunodeficiency and lead to infections due to P. carinii, Candida, mycobacteria, or other organisms. (3 Refs)

29. KAPOSI'S SARCOMA (KS) IN LYMPH NODES OF A PATIENT WITH CYTOMEGALOVIRUS (CMV) VIREMIA (MEETING ABSTRACT)

Gyorkey F, Sinkovics JG, Luchi RJ, Small SD, Craig P, Rossen R, Gyorkey P, Melnick JL
Veterans Administration Medical Center and Baylor College of Medicine, Houston, TX, 77211
Proc Am Assoc Cancer Res; 23:1106 1982

A 34 yr old homosexual man developed fever, lymphadenopathy and hepatosplenomegaly. He was a long term user of phenytoin. Lymph node pathology showed KS. Vascular endothelial cells, hepatocytes and lymphocytes contained an abundance of cytoplasmic tubuloreticular structures identical with those described by us in lupus and in interferon-treated human lymphoblasts by Rich. Pneumocystis carinii was found by lung biopsy. Giardia lamblia was present in his intestines. CMV was isolated from urine, liver and lung, and also identified by electron microscopy in the biopsy and autopsy tissues. Hypoglobulinemia and depressed cell-mediated immunity were documented. Postmortem, Cryptococcus species was found in some lymph modes in addition to KS. (2 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

30. MALIGNANT MELANOMA AND DRINKING WATER CONTAMINATION.

Aldrich TE, Peoples AJ
Dept. Epidemiology and Public Health, Univ. Miami Sch. Medicine, Miami, FL, 33101
Bull Environ Contam Toxicol; 28(5):519-523 1982

A cluster analysis of data on the incidence of melanoma in three areas of Brevard County, Florida, showed a north-south gradient, with a significantly increased number of new melanoma cases in South Brevard County in 1979 compared to the expected values calculated using the Third National Cancer Survey data. An analysis of municipal water samples for trihalomethane (THM) levels (chloroform, bromoform, chlorodibromomethane, and bromodichloromethane) showed a similar north-south gradient with a marked increase in THM levels in South Brevard County. These results may indicate a possible etiologic relationship between melanoma and THM exposure. (9 Refs)

31. A RE-EXAMINATION OF THE ROLE OF SOLAR RADIATION IN THE ETIOLOGY OF CUTANEOUS MALIGNANT MELANOMA (MEETING ABSTRACT)

Schwartzbaum J
Division of Epidemiology, School of Public Health, University of California Los Angeles, Los Angeles, CA
109th Annual Meeting of the American Public Health Association, November 1-5, 1981, Los Angeles, California. American Public Health Association 390 pp., 1981.

Age-adjusted incidence and mortality rates of cutaneous malignant melanoma are rising at the rate of 3% per year. Epidemiologists have attributed this secular trend to alterations in the percentage of the body covered by clothing and the subsequent increased exposure to ultraviolet radiation. Using incidence data from the Connecticut Tumor Registry (1935-1978) and the methods of content analysis to create indices of changes in the percentage of the body covered by clothing, I constructed a mathematical model which takes age, period, and cohort effects into account to investigate the association between changes in incidence rates and changes in fashion. Preliminary results indicate a statistically significant association. I evaluate these results in the context of the issues related to the use and interpretation of aggregate data. (no Refs)

32. RISK FACTORS FOR KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Marmor M, Laubenstein L, William DC, Friedman-Klen AE, Byrum RD, D'Onofrio S, Dubin N
Inst. Environmental Medicine, New York Univ. Medical Center, 341 East 25th St., New York, NY, 10010
Lancet; 1(8281):1083-1087 1982

An investigation of 20 homosexual men with histologically confirmed Kaposi's sarcoma and 40 controls revealed significant associations between Kaposi's sarcoma and use of a number of drugs (amyl nitrite, ethyl chloride, cocaine, phencyclidine, methaqualone, and amphetamine), history of mononucleosis, and sexual activity in the yr before onset of the disease. Patients with Kaposi's sarcoma also reported substantially higher rates of sexually transmitted infections than did controls. Multivariate analysis indicated independent significant associations for amyl nitrite and sexual activity and showed use of phencyclidine, methaqualone, and ethyl chloride to be nonsignificant. Evaluated at the median exposure for patients, the analysis yielded risk-ratio estimates of 12.3 for amyl nitrite (95% confidence limits 4.2, 35.8) and 2.0 for sexual activity (95% confidence limits 1.3, 3.1). (Author abstract) (21 Refs)

SELECTED PRECLINICAL STUDIES

33. HUMAN TRANSFORMING GROWTH FACTOR. PRODUCTION BY A MELANOMA CELL LINE, PURIFICATION, AND INITIAL CHARACTERIZATION.

Marquardt H, Todaro GJ
Lab. Viral Carcinogenesis, NCI, NIH, Frederick, MD, 21701
J Biol Chem; 257(9):5220-5225 1982

A low mol wt human transforming growth factor (hTGFs) was isolated from serum-free medium conditioned by a human metastatic melanoma tumor line, A2058. The purification of hTGFs was achieved by gel permeation chromatography of the acid-soluble growth-promoting activity on Bio-Gel P-10 in 1 M acetic acid, followed by reverse phase high pressure liquid chromatography on muBondapak C18 support using a linear gradient of acetonitrile in 0.045% trifluoroacetic acid, and subsequently by rechromatography of the human transforming growth factor-containing fractions with a linear 1-propanol gradient in 0.035% trifluoroacetic acid on the same column. The estimated mol wt of hTGFs is 7,400. It is a single chain polypeptide with three intrachain disulfide bridges and no free sulfhydryl groups. Lacking tyrosine and methionine, but containing three phenylalanine residues, hTGFs is unlike human and mouse epidermal growth factor (EGF). hTGFs competes with 125I-labeled EGF for binding to A431 human carcinoma cells completely and equivalently, and thus is functionally related to EGF. In contrast, hTGFs enabled normal anchorage-dependent rat kidney cells to grow in soft agar, whereas EGF did not stimulate growth of these cells in semisolid medium. The half-maximal growth-stimulating response of htGFs was reached with one EGF-competing unit or 1.1 ng of hTGFs. (Author abstract) (24 Refs)

34. AGENTS WITH POTENTIAL SPECIFICITY AGAINST MELANOTIC MELANOMA.

Lin AJ, Kelley JA, Breitman TR, Driscoll JS
Lab. Medicinal Chemistry and Biology, NCI, NIH, Bethesda, MD, 20205
J Med Chem; 25(5):501-505 1982

Agents were designed to exploit the high tyrosinase activity in melanotic melanoma relative to normal tissues. If specific tyrosinase activation of these agents occurred, the production of toxic metabolites in the melanoma cells would produce selective cell kill. Synthesis and antitumor activities of three new amino acids, (1a) [beta-[(p-hydroxyphenyl)amino]alanine hydrochloride], (1b) [Ndelta -(p-hydroxyphenyl)ornithine hydrochloride], and (1c) [Ndelta-(m-hydroxyphenyl)ornithine dihydrochloride], were described. Compounds 1a and 1b were approx two-fold more active against the B-16 melanotic melanoma than the amelanotic melanoma cell line in vitro. Compound 1b was approx two-fold more potent than compound 1a against either cell line and was eight-fold more potent than L-glutamic acid gamma-(4-hydroxyanilide), a natural product isolated from mushroom. No significant growth inhibitory activity was found for the m-hydroxy analogue 1c at 100 uM, the highest concentration tested. Similarly, compound 1b exhibited better activity against P-388 (ED50 = 9.5 x 10(-6) M) than 1a (ED50 = 3.2 x 10(-5) M) and was about 30-fold more potent than 1c. Against human epidermoid carcinoma of the nasopharynx (KB), these agents showed modest inhibitory activity with ED50 values in the range of 1.2 to 3 x 10(-4) M. No in vivo activity against P-388 and B-16 at doses up to 150-200 mg/kg was observed. The biological results suggest that a nonspecific oxidation rather than a specific tyrosinase activation is involved in the biological action of these new compounds. (Author abstract) (21 Refs)

35. COLONY GROWTH AND CHEMOSENSITIVITY IN VITRO OF HUMAN MELANOMA BIOPSIES. RELATIONSHIP TO CLINICAL PARAMETERS.

Tveit KM, Fodstad O, Lotsberg J, Vaage S, Pihl A
Norsk Hydro's Inst. for Cancer Res., Montebello, Oslo 3, Norway
Int J Cancer; 29(5):533-538 1982

To study the usefulness of an in vitro colony-forming assay in predicting individual clinical responses to chemotherapy, tumor cells obtained from 150 melanoma metastases (119 patients) were grown in soft agar according to the method of

Courtenay and Mills (1978), and tested for sensitivity to dacarbazine, lomustine, vinblastine, procarbazine, abrin, and ricin. In 83% of the cases colony formation was observed (plating efficiency, PE, greater than 0.01%). Twenty-seven per cent of the tumors gave PEs greater than or equal to 1%, 45% gave PEs in the range 0.1-0.9%, whereas 11% of the tumors gave 0.01-0.09%. The PEs were not correlated with the degree of pigmentation or with the clinical course. Evaluable chemosensitivity data were obtained on 104 metastases from 83 patients. Large differences in sensitivity were seen. In cases which were evaluable both in vivo and in vitro a clear correlation was found between the in vitro chemosensitivity, expressed as the expected growth delay, and the clinical response to chemotherapy. Tumors from patients with partial response, mixed response or stable disease after prior progression, all had rather high in vitro sensitivity to the drug used (expected growth delay greater than or equal to 2.0), whereas patients with progression had lower sensitivity. The results confirm that the soft agar method used here provides good culture conditions for human melanoma cells and show that chemosensitivity data can be obtained in a high percentage of melanoma patients. The approach used seems promising in aiding clinicians to adjust chemotherapy to individual patients. (Author abstract) (20 Refs)

36. INFLUENCE OF ANXIETY STRESS AND ADRENAL CORTICOIDS UPON THE INCIDENCE OF MELANOMA METASTASES (MEETING ABSTRACT)

Riley V, Fitzmaurice MA
Fred Hutchinson Cancer Research Center, Seattle, WA, 98104
Proc Am Assoc Cancer Res; 23:926 1982

The purpose of these studies was to examine the influence of controlled anxiety stress upon the incidence and number of metastases transmitted from a distant growing tumor to susceptible organs. In contrast to the study of tumor foci occurring at various locations following the intravenous inoculation of cancer cell suspensions, we have employed a more realistic model utilizing a transplantable B-16 mouse melanoma as a solid subcutaneous tumor. Under circumstances having to do with psychoneuroimmunologic forces this tumor is capable of metastasizing to the lungs and the intestines. The resulting metastatic lesions can be quantified by a double petri dish compression of the removed lungs or intestines to provide a flat optical field suitable for accurate metastases counts. The black metastatic foci can be readily counted with either the naked eye or with the aid of a dissecting microscope. Controlled, quantifiable anxiety stress was induced by slow-speed, intermittent rotation; or, its biochemical equivalent was simulated by the direct implantation of stress-associated corticosterone, or other corticoids, administered in an insoluble, slow-release form. Thus, either endogenous or exogenous corticoids increased metastatic spread. A typical example of the differences in metastatic incidence found between low-stress control mice and those subject to mild rotation-stress was: Controls 40%; Stress-rotation 90%; Exogenous corticosterone 100%. Prednisone also increased metastatic spread. (1 Ref)

37. INTERFERON INCREASES HLA SYNTHESIS IN MELANOMA CELLS: INTERFERON-RESISTANT AND -SENSITIVE CELL LINES.

Basham TY, Bourgeade MF, Creasey AA, Merigan TC
Div. Infectious Diseases, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Proc Natl Acad Sci USA; 79(10,part1):3265-3269 1982

We report that human leukocyte interferon preparations increase the expression of beta2-microglobulin by 100-200% on the surface of normal fibroblast and melanoma cell lines sensitive to interferon. This increase in expression can be correlated with an increase in HLA synthesis as measured by incorporation of [35S]methionine in these antigens. This enhanced HLA synthesis, which is 5-to 17-fold, is time dependent and dose related. Synchronized cells in the G0/G1 phase of the cell cycle appear to be more sensitive to this interferon action. Neither an increase in surface expression nor in HLA synthesis is observed in a melanoma cell line resistant to the antiviral and antigrowth effects of interferon. Furthermore, there appears to be a stronger correlation between this increased HLA synthesis and the antiviral function that between it and the antiproliferative action of interferon. (Author abstract) (18 Refs)

38. BIOLOGIC PROFILE OF HUMAN MELANOMA CELL ANTIGENS (MEETING ABSTRACT)

Wolf P, Ferrone S
Department of Pathology, University of California, and Scripps Clinic and Research Foundation, La Jolla, CA
Lab Invest; 46(1):91A 1982

Monoclonal xenoantibodies to a cytoplasmic and to a membrane-bound tumor-associated antigen in human melanoma cells have been produced. Analysis with cultured human cell lines and with surgically removed tumor tissues indicates that the plasma membrane antigen is restricted to melanoma, whereas the cytoplasmic antigen is synthesized by tumor cells of various histologic types. The membrane-bound antigen, is an efficient target of antibody-mediated lysis of melanoma cells. The cytoplasmic antigen which consists of four glycopolypeptides of 94,000, 75,000, 70,000, and 25 daltons, is readily shed by tumor cell lines into the spent culture medium. Human melanoma cells have also unexpectedly been found to express Ia-like antigens. Melanoma derived Ia-like antigens are immunologically functional. Monoclonal antibodies have also been produced to these antigens. The level of Ia-like antigens on melanoma cells is significantly lower than on B lymphoid cells, and this is likely to reflect a reduced synthesis more than an increased shedding. Melanoma cell-derived Ia-like antigens have a structure similar to that of B lymphoid cell-derived Ia-like antigens. The antigens are composed of two noncovalently associated glycoproteins. One chain, the alpha chain, has an approximate molecular weight of 34,000 and the other one, the beta chain, has an approximate molecular weight of 29,000. We have studied benign and malignant melanocytic skin lesions with our monoclonal antibody to Ia-like antigens and have found that the expression of Ia-like antigens is restricted to malignant melanoma. (no Refs)

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DIAGNOSIS

1. THE PATHOLOGY OF HEAD AND NECK TUMORS: MUCOSAL MELANOMAS, PART 13.

Batsakis JG, Regezi JA, Solomon AR, Rice DH
Dept. Pathology, M. D. Anderson Hosp. and Tumor Inst., Texas Medical Center, Houston, TX, 77030
Head Neck Surg; 4(5):404-418 1982

Incidence and etiologic and pathogenetic bases for mucosal melanomas are reviewed, and characteristics of related pigmented lesions are discussed. Respiratory tract melanomas arise almost exclusively in the upper portion from melanocytes normally present in the mucosa of the nasal cavity, paranasal sinuses, and larynx. Oral pigmentation varies according to the race of the individual, and is much more common in hosts with darker skin such as blacks, Orientals, and residents of the Mediterranean basin. The most common exogenous and iatrogenic reason for nonmelanocytic pigmentation of oral mucosa is the deposition of dental amalgam. Melanocytic macules are lesions with clinicopathologic correlation between a clinically discrete pigmented macule and histologic features of hyperpigmentation of the basal-cell layer or lamina propria or both. Nearly every form of cutaneous nevus can present as an in-

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traoral lesion, but significant differences exist in the types of nevi found in the oral cavity. Within the oral cavity, the palate and alveolar gingivae are the most common sites of predilection for melanomas; nearly 80% of oral melanomas arise in the mucosa of the upper jaw, with the majority occurring on keratinizing mucosa. Prognostic indicators for mucosal melanomas of the head and neck have been difficult to establish. Although melanomas of the upper aero-digestive tract are much less common than cutaneous melanomas, the fatality rate is nearly always greater. (51 Refs)

2. FLOW CYTOFLUOROMETRIC DNA ANALYSES OF METASTASES OF HUMAN MALIGNANT MELANOMAS.

Hansson J, Tribukait B, Lewensohn R, Ringborg U
(c/o Tribukait) Dept. Medical Radiobiology, Karolinska Sjukhuset and Institutet, Box 60204, S-104 01 Stockholm 60, Sweden
Anal Quant Cytol; 4(2):99-104 1982

Flow cytofluorometric analyses of DNA content were performed on 38 subcutaneous and lymph node metastases from 32 patients with malignant melanoma. Thirty tumors yielded only one cell population, and eight tumors contained two or more populations. Seven tumors contained two different aneuploid cell populations, whereas one had five different cell populations. Diploid cells, which may have represented an additional tumor cell population, were found in some tumors. DNA content varied from 1.2n to 9.0n (normal human lymphocyte 2n standard). Eight tumors contained a single cell population with DNA content equal to control cells; five tumors contained a hypodiploid population. Two of these tumors had one hypodiploid population each; a third contained two hypodiploid populations; two others contained both hypo- and hyperdiploid populations. No difference was found between cell populations from different metastases in the same patient in five cases. S-phase cells numbers were analyzed in populations obtained from 25 metastases from 21 patients who had received no prior chemotherapy. The proportions of S-phase cells varied from 3-34%, usually being 5-15%. Proportions of S-phase cells in more than one metastasis from each of three patients showed differences in the number of metastases between different metastases in the same patient. No significant correlation was observed between DNA content and number of S-phase cells in 26 cell populations. Patients with more than or equal to 10% S-phase cells in their metastases survived significantly longer than those with less than 10% S-phase cells. Cellular DNA content above or below 2.5n was not significantly related to survival from time of discovery of first metastasis. (22 Refs)

3. HORMONAL STATUS OF PATIENTS WITH PRIMARY MALIGNANT MELANOMA: A REVIEW OF 313 CASES.

Danforth DN, Russell N, McBride CM
(c/o McBride) Dept. Surgery, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
South Med J; 75(6):661-664 1982

We studied 313 patients with a confirmed diagnosis of primary malignant melanoma who presented to the University of Texas System Cancer Center between 1976 and 1980, to determine the relationship of endocrine status to the presentation of this tumor. There were 171 women and 142 men, a ratio of 1.20:1. Age, age range, race, and residence distribution were comparable for both sexes. The women married and had their first pregnancy at ages at least comparable to the population in general. They tended to have multiple pregnancies (av, 2.64), to nurse their children, to have an aggregate 32 yr of menstrual activity, and to use exogenous hormones (73%). The female patients in this study had more favorable lesions than their male counterparts in all five microstaging categories: type of melanoma, location, level of invasion, thickness, and stage. Analysis of the hormonal subgroups among the women revealed the morphology of the primary tumor to be independent of menopausal status, parity, or the use of exogenous hormones. These findings suggest that hormonal background does not effect the acquisition of malignant melanoma, but may influence its subsequent spread. (Author abstract) (17 Refs)

4. FACTORS PROGNOSTIC FOR SURVIVAL IN PATIENTS WITH MALIGNANT MELANOMA SPREAD TO THE REGIONAL LYMPH NODES.

Callery C, Cochran AJ, Roe DJ, Rees W, Nathanson SD, Benedetti JK, Elashoff RM, Morton DL
(c/o Cochran), Univ. Los Angeles Sch. Medicine, 9th Floor, Factor Building, Los Angeles, CA, 90024
Ann Surg; 196(1):69-75 1982

To establish clinical and histologic determinants of survival, records of all UCLA patients with resectable melanoma metastatic to the lymph nodes during the yr 1954-1976 were reviewed. These 150 patients were treated first with wide excision, lymphadenectomy, and with radiation/chemotherapy and/or additional surgery only if further recurrences developed. None received adjuvant immunotherapy or chemotherapy. In 97 of 139 patients with identified primary tumors, slides of the primary lesion were reviewed. Putative prognostic factors included age, sex, parity, site of primary tumor, presence of satellitosis, clinical status of nodes, histologic characteristics of primary lesion (Clark's level, thickness of tumor, presence/width of ulceration, and number of mitoses/HPF), time from biopsy of primary tumor to lymphadenectomy, and number of positive nodes. Kaplan-Meier estimates of survival for the entire group at 1, 2, 5, and 10 yr were 73, 55, 37, and 33%, respectively. Median follow-up period of survivors was 4 yr. Univariate analyses using the log-rank test showed that thickness of the primary lesion (p less than 0.001), width of ulceration ($p = 0.005$), absence of ulceration ($p = 0.024$), and number of positive nodes ($p = 0.033$) were prognostic for survival. In multivariate analysis by the Cox procedure, thickness of the primary ($p = 0.001$) and number of melanoma-containing nodes ($p = 0.043$) were prognostic for survival. Location of the primary tumor became marginally significant ($p = 0.12$) in the multivariate model. These findings demonstrate the prognostic importance of characteristics of both the primary lesion and extent of regional dissemination. Future prospective randomized trials for (adjuvant) therapy for Stage II melanoma should be stratified by these variables. (Author abstract) (26 Refs)

5. MALIGNANT MELANOMAS OF THE HUMAN UVEA. TWENTY-FIVE YEAR FOLLOW-UP OF CASES IN DENMARK, 1943-1952.

Jensen OA
Eye Pathology Inst., Univ. Copenhagen, Frederik V's Vej 11, 5, DK-2100, Copenhagen, Denmark
Acta Ophthalmol (Copenh); 60(2):161-182 1982

A follow-up of 302 patients who underwent enucleation for malignant intraocular melanoma between 1943-1952 is presented. These patients constituted the entire population of men and women treated for intraocular melanoma in Denmark during this period. A follow-up of 99% was achieved, 82% of the total being dead at the time of the followup. Of follow-up survivors, one patient with previous orbital recurrence was alive.

The remaining survivors had no orbital recurrence or signs of metastases. Slightly more than half of patients dead at the time of follow-up were found to have died as a result of metastases. Slit lamp examination of the orbit to detect remaining malignant cells is recommended. In the event of recurrence conservative exenteration with preservation of the eyelids and periosteum is advised. In the few cases in which the eyelids are invaded, a regular exenteration is recommended. Prognosis in relation to various histopathological parameters, and therapy are also discussed. (48 Refs)

6. THE INCIDENCE OF METASTASES FROM UNTREATED CILIARY BODY AND CHOROIDAL MELANOMA.

Wagoner MD, Albert DM
(c/o Albert) Howe Lab. Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA, 02114
Arch Ophthalmol; 100(6):939-940 1982

A large survey was conducted to identify patients with choroidal and ciliary body melanomas in whom preoperative evaluation for the presence of metastases was performed. Twenty-nine (2.47%) of 1,214 patients were found to have metastases prior to surgical manipulation of the globe. Liver function enzymes combined with liver-spleen scanning is the most effective means for screening for the presence of metastases in these patients and should be performed in all cases in which surgical manipulation of the globe is anticipated. (Author abstract) (9 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

7. HETEROGENEITY OF MELANOMA-ASSOCIATED ANTIGENS DETECTED BY SERA FROM PATIENTS RECEIVING ADJUVANT ALLOGENEIC TUMOR VACCINE IMMUNOTHERAPY.

Dent PB, McCulloch PB, Liao SK, Stone BR, Singal DP
Dept. Pediatrics, Internal Medicine and Pathology, McMaster Univ., Ontario Cancer Treatment and Res. Foundation, Hamilton Clinic, Hamilton, Ontario L8N 3Z5, Canada
Clin Immunol Immunopathol; 23(2):379-391 1982

Sera from 40 patients with malignant melanoma entered into a randomized controlled trial of nonspecific and specific active immunotherapy were studied for the presence of melanoma-specific IgG antibody. Reactivity was revealed by mixed hemadsorption assay against a panel of 10 cultured melanoma cell lines. Prior to therapy 3 of 40 patients had antibody to one or more melanoma lines which in all cases was eliminated by absorption with platelets or colon carcinoma cells. After 6 mo of therapy patients in the group not receiving tumor vaccine had no absorption-resistant antimelanoma reactivity. However all 10 patients receiving allogeneic tumor vaccine had high titered melanoma reactivity which in 8 patients was not removed by platelet or carcinoma absorption. Three patients reacted only against melanoma targets while of the remaining five patients, four reacted against cultured brain tumor cells supporting previous suggestions of a possible antigenic cross-reactivity among tumors of neuroectodermal origin. Clinical outcome was not correlated with the presence of antibody to melanoma target cells. Persistance of antibody was dependent on continued vaccine administration suggesting that rather than being an index of resistance, the presence of antibody may be a marker for the presence of tumor. Sera from alloimmunized melanoma patients identify a heterogeneous complex of melanoma-associated surface antigens. More information about the serological and immunological properties of these antigens is required to determine if these responses are clinically relevant. (Author abstract) (21 Refs)

8. FLOW CYTOFLUOROMETRIC DETECTION OF TUMOR-SPECIFIC ROSETTE-FORMING CELLS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK.

Tong AW, Vandenbark AA, Kraybill W, Vetto RM, Burger DR
Dept. Microbiology, Oregon Health Sciences Univ., Portland, OR, 97207
Cancer Res; 42(7):2949-2955 1982

Tumor-specific rosette-forming cells reactive to solubilized tumor antigens conjugated to autologous erythrocytes were quantitated by flow cytofluorometry. Leukocytes from a high frequency of the patients (greater than 70%) with squamous cell carcinoma of the head and neck (SQCC) formed rosettes to the conjugated SQCC tumor antigens but not to other histologically distinct tumor antigens (melanoma and colon carcinoma). Healthy control subjects or tumor patients with other cancers were mostly unreactive to the SQCC tumor extract [1 of 21 (5%) and 1 of 14 (7%) for controls and tumor patients, respectively]. Rosette-forming activity was observed in SQCC patients with primary cancers [22 of 30 (73%)] or in remission [5 of 6 (83%)], whereas patients with tumor recurrence were uniformly unresponsive. Tumor-specific rosette formation was mediated predominantly by monocytes, as identified by histochemical techniques and physiological properties. Rosette formation in reactive patients was abrogated by short-term culture, but the abated response could be restored by incubation with autologous serum or sera from other rosette-forming cell-positive patients. However, responsiveness of nonreactive patients with SQCC recurrence could not be constituted by rosette-forming cell-positive sera. These observations suggested the presence of tumor-reactive monocytes in a high frequency of patients with primary cancer or in remission but not in patients with recurrent disease. (Author abstract) (28 Refs)

9. HLA COMPLEX AND FAMILIAL MALIGNANT MELANOMA.

Pellegris G, Illeni MT, Rovini D, Vaglini M, Cascinelli N, Ghidoni A
Istituto Nazionale per lo Studio e la Cura dei Tumori, via Venezian 1, 20133 Milan, Italy
Int J Cancer; 29(6):621-623 1982

Six families with familial malignant melanoma (FMM) were HLA-A, -B, and -C typed to ascertain whether or not FMM would segregate with the HLA complex. The HLA-B12 antigen was present in five of the six families. In three families the HLA-FMM linkage could be analyzed: linkage was possible in two but not in the third. These findings suggested that two types of FMM may exist: a more frequent type (5 cases) that apparently segregates with the HLA complex and another (1 case) that does not segregate with the HLA complex. Moreover, a factor included in the HLA region or another factor linked to it may have played an important role, in five of the six families, in FMM pathogenesis, whereas in the sixth family its role may have been performed by some other factor. These findings are consistent with the hypothesis of two complementary factors (1 of which was included in the HLA complex) for the promotion of FMM with dominant inheritance and high penetrance. (Author abstract) (10 Refs)

CHEMOTHERAPY

10. PHASE II TRIAL OF TAMOXIFEN IN MALIGNANT MELANOMA.

Leichman CG, Samson MK, Baker LH
(c/o Samson) Dept. Oncology, Univ. Health Center, 4201 St. Antoine 7-C, Detroit, MI, 48201
Cancer Treat Rep; 66(6):1447 1982

A phase II clinical trial of tamoxifen (TO) in disseminated malignant melanoma with a standard dose of 10 mg TO po bid was conducted in 20 patients (9 females, 11 males, 34-81 yr old, median 51 yr). All but two patients had received previous chemotherapy or immunotherapy; most had been treated with multiple drugs, either dacarbazine alone or in combination. Disease-free interval ranged from zero (disseminated at diagnosis) to 8 yr (median, 25 mo). Median Karnofsky performance status at the time of entry into the protocol was 80 (range 40-100). Of the 20 patients studied, 16 had predominantly soft tissue disease, 3 had lung disease, and 1 had lung and soft tissue disease. Nine patients had negative estrogen receptor protein assays, and two had 'low': 3.6 and 4.0 femtomole/10 mg wet wt of tissue. Eighteen patients were evaluable for response. One patient had a partial response after 4 wk of treatment, with regression of skin nodules. The response lasted for 3 wk prior to appearance of new disease. The estrogen receptor protein was negative in the patient. Toxic reactions were rare and consisted of mild nausea, wt gain, and hot flashes. Results of the study indicated that TO is not an effective agent in the treatment of disseminated malignant melanoma in patients who have received prior chemotherapy. (5 Refs)

11. PHASE II TRIAL OF CHLOROZOTOCIN IN MALIGNANT MELANOMA, BREAST CANCER, AND OTHER SOLID TUMORS.

Silver BA, Barlock AL, Lippman ME, Anderson T, Fisher RI
(c/o Fisher) Medicine Branch, Div. Cancer Treatment, NCI, NIH, Building 10, Room 12N226, Bethesda, MD, 20205
Cancer Treat Rep; 66(5):1229-1230 1982

We have conducted a broad Phase II clinical trial of chlorozotocin in 74 patients including 28 with malignant melanoma, 18 with breast cancer, 9 with non-Hodgkin's lymphoma, 6 with nonseminomatous testicular cancer, 5 with ovarian cancer, 4 with sarcoma, 3 with non-beta islet cell carcinoma of the pancreas, and 1 with anaplastic carcinoma of the thyroid. Objective responses were noted only in 15% of the patients with melanoma and in 11% of the patients with non-Hodgkin's lymphoma. Significant leukopenia and thrombocytopenia were observed only in previously treated patients. Chlorozotocin does not appear to offer clinically significant advantages over other currently available nitrosoureas. (Author abstract) (14 Refs)

12. COMBINATION CHEMOTHERAPY PLUS BCG IN THE TREATMENT OF DISSEMINATED MALIGNANT MELANOMA: A SOUTHWEST ONCOLOGY GROUP STUDY.

Costanzi JJ, Al-Sarraf M, Groppe C, Bottomley R, Fabian C, Neidhart J, Dixon D
MW 414, Univ. Texas Medical Branch, Galveston, TX, 77550
Med Pediatr Oncol; 10(3):251-258 1982

The Southwest Oncology Group performed a randomized study comparing combination chemotherapy alone vs combination chemotherapy plus BCG vs dacarbazine plus BCG in the treatment of disseminated malignant melanoma. A 31% response rate was noted with combination chemotherapy alone, a 27% response rate with combination chemotherapy plus BCG, and an 18% response rate with DTIC plus BCG. Survival was not influenced by type of therapy, but the responders had significantly longer survival than the nonresponders. There appeared to be some significant differences in response as related to age wherein those patients between the ages of 30 and 60 yr had a higher response rate to combination chemotherapy as compared to DTIC plus BCG. Those patients older than 60 yr of age had a higher response rate in the BCG groups. Furthermore, in those patients older than 60 yr of age who responded, their duration of response was longer if they received BCG than those who did not receive BCG. It should be emphasized that those differences noted in various age groups could occur by chance alone. These differences should be studied in the future, by appropriate pretreatment stratifications. Patients with higher peripheral lymphocyte counts had significantly better response rates and those patients with higher numbers of positive delayed hypersensitivity skin tests had significantly greater survival. A significant improvement in survival was noted in patients whose PPD converted from negative to positive during therapy. (Author abstract) (11 Refs)

13. ACTIVITY OF ISOTRETINOIN AGAINST SQUAMOUS CELL CANCERS AND PRENEOPLASTIC LESIONS.

Meyskens FL, Gilmartin E, Alberts DS, Levine NS, Brooks R, Salmon SE, Surwit EA
Dept. Internal Medicine, Section Hematology and Oncology, Univ. Arizona, Health Sciences Center, 6th Floor Facility, Tucson, AZ, 85724
Cancer Treat Rep; 66(6):1315-1319 1982

We investigated the effect of the synthetic vitamin A derivative isotretinoin (13-cis-retinoic acid) on advanced cancers in 103 patients and on preneoplastic lesions in five patients. Six of 14 patients with squamous cell epithelial cancers had objective regressions of skin or subcutaneous metastases. Three of five patients with preneoplastic lesions had objective responses. The major dose-limiting toxic effects were reversible dermatitis, emotional lability, and headaches. We conclude that the growth of some squamous cell epithelial malignancies can be inhibited by isotretinoin and suggest that other retinoids should be evaluated as antitumor agents. (Author abstract) (31 Refs)

RADIOTHERAPY

14. HELIUM ION THERAPY FOR CHOROIDAL MELANOMA.

Char DH, Castro JR, Stone RD, Irvine AR, Barricks M, Crawford JB, Schatz HA, Lonn LI, Hilton GF, Schwartz A, Quivey JM, Saunders W, Chen GT, Lymon JT
Ocular Oncology Unit, S-315, Univ. California, San Francisco, CA, 94143
Arch Ophthalmol; 100(6):935-938 1982

Forty patients with choroidal melanomas received radiation therapy with helium ion-charged particles. Thirty-six of 40 patients either remained stable or demonstrated tumor shrinkage. Seventeen of 18 patients followed up for at least 1 yr after therapy demonstrated tumor regression, with a mean tumor shrinkage of approx 40%. The most effective method of choroidal melanoma management is unclear. Charged-particle external-beam irradiation may be more applicable and have less ocular morbidity than either radioactive plaques or photocoagulation. (Author abstract) (20 Refs)

OTHER THERAPEUTIC MODALITIES

15. THE ROLE OF CRYOTHERAPY IN THE MANAGEMENT OF CONJUNCTIVAL MELANOMA.

Jakobiec FA, Brownstein S, Albert W, Schwarz F, Anderson R
Manhattan Eye, Ear and Throat Hosp., 210 East 64th St., New York, NY, 10021
Ophthalmology (Rochester); 89(5):502-515 1982

The use of cryotherapy in the treatment of 15 patients (10 women, 5 men) with melanocytic proliferative disease of the conjunctiva is described. Five patients were treated who had involvement of extensive geographic zones of either bulbar, palpebral, canthal, forniceal, or plical-caruncular conjunctiva by flat pigmentation. Of these, three have retained virtually the same pre- and postoperative visual acuities, without motility restrictions or extensive symblepharon formation. While only two are cured, the other three require only modest therapy to stay ahead of their disease. Four patients had nodules of invasive melanoma that were accompanied by insignificant amounts of surrounding flat pigmentation. Cryotherapy was added to the management protocol after surgical resection. None of these patients developed recurrence. Six patients had one or more nodules of invasive conjunctival melanoma associated with extensive areas of flat pigmentation involving various regions of the epibulbar, forniceal, tarsal-palpebral, canthal, and plical-caruncular conjunctiva. The corneal epithelium was frequently stippled with pigment. Two of these patients were treated with a single cryotherapy, but the other four required two or more treatments. Three of these six experienced complete eradication of their disease, established by biopsy, with follow-up of 3 mo, 9 mo, and 3 yr. The rationale, methods, limitations, results, and complications of cryotherapy are discussed. (13 Refs)

CASE REPORTS

16. RECURRENT MALIGNANT MELANOMA PRESENTING AS MONOARTHRITIS.

Shenberger KN, Morgan GJ
Arthritis Center, Dartmouth-Hitchcock Medical Center, Hanover, NH, 03755
J Rheumatol; 9(2):328-330 1982

A case of metastatic carcinomatous arthritis in a 29-yr-old female is reported; the monoarthritis was associated with 4 mo of right knee pain occurring approx 4 yr after the patient had had resection of a malignant melanoma Clark's Level IV of the right medial calf. Recurrence of Level IV cutaneous melanoma is likely; apparently it may manifest itself as metastatic carcinomatous arthropathy. (13 Refs)

17. STURGE-WEBER DISEASE. THE VALUE OF A TOPOGRAPHIC ANALYSIS OF A FACIAL ANGIOMA IN THE DIAGNOSIS OF ASSOCIATED PIAL ANGIOMA.

Dulac O, Larregue M, Roger J, Arthuis M
Hopital Saint-Vincent-de-Paul, 74, av. Denfert-Rochereau, 75674 Paris, France
Arch Fr Pediatr; 39(3):155-158 1982

Locations at facial angiomas were correlated with the existence of pia mater angiomas (PMA) in 47 children with congenital capillary nevi of the face. When the whole face was involved, 3/4 children had PMA as revealed by computed tomography. All 21 children with dermatologic angiomas of the eyelid, forehead, and cheek had PMA. All three children with angiomas confined to the base of the nose had PMA. (14 Refs) (In FRE)

18. NEVOID BASAL CELL CARCINOMA SYNDROME AND EPILEPSY.

Murphy MJ, Tenser RB
Dept. Neurology, Univ. Hosp., Iowa City, IA, 52242
Ann Neurol; 11(4):372-376 1982

The cases of four patients (3 male, 1 female, 9-29 yr old) with recurrent seizures associated with nevoid basal cell carcinoma (NBCC) are described. Three patients were members of a kinship with documented NBCC syndrome in four generations; other members of the family had nonfebrile seizures during childhood. The case history of the fourth patient is detailed. The patient had recurrent generalized seizures and severe mental retardation from the age of 2 yr. At age 12 yr, many small papular lesions were noted over the face and dorsum of the hands, and a cafe-au-lait spot was found on the back. Five yr later the patient developed an expanding lesion in the anterior mandibular area. Biopsy of mandibular cysts was diagnostic of odontogenic cysts. At age 25 multiple brownish papular skin lesions were scattered over the face, shoulders, back, forearms, and legs. Single, firm, sc nodules were palpable in the jaw, calf, and volar aspects of both arms. Seizures occurred two or three times per yr. Biopsies of skin lesions disclosed dermal nevi and basal cell carcinoma. Family history was positive for documented nevoid basal cell carcinoma syndrome: NBCC was present in the father and two sisters. Reported cases of NBCC associated with seizure are reviewed. (24 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

19. FAMILIAL MELANOMA ASSOCIATED WITH DOMINANT ULTRAVIOLET RADIATION SENSITIVITY.

Ramsay RG, Chen P, Imray FP, Kidson C, Lavin MF, Hockey A
(c/o Kidson) Queensland Inst. Medical Res., Brisbane 4006, Australia
Cancer Res; 42(7):2909-2912 1982

Sensitivity to ultraviolet radiation was studied in lymphoblastoid cell lines derived from 32 members of two families with histories of multiple primary melanomas in several generations. As assayed by colony formation in agar or by trypan blue exclusion following irradiation, cellular sensitivity showed a bimodal distribution. All persons with melanoma or multiple moles were in the sensitive group, while some family members exhibited responses similar to those of controls. Cells from four cases of sporadic melanoma showed normal levels of sensitivity. The data are consistent with a dominantly inherited ultraviolet light sensitivity associated with these examples of familial melanoma. Spontaneous and ultraviolet light-induced sister chromatid exchange frequencies were similar to those in control cell lines. No defect in excision repair was detected in any of the above cell lines, but the sensitive group showed postirradiation inhibition of DNA replication intermediate between controls and an excision-deficient xeroderma pigmentosum cell line. (Author abstract) (25 Refs)

20. KAPOSI'S SARCOMA - AN EMERGING EPIDEMIC.

Mansell PW

Div. Cancer Prevention, M. D. Anderson Hosp. and Tumor Inst., Houston, TX

Cancer Bull; 34(2):72-74 1982

The pathobiology of Kaposi's sarcoma and the recent outbreak of the disease (greater than 200 cases) that has occurred among young male homosexuals are described. Kaposi's sarcoma may be associated with the DNA virus cytomegalovirus. It is also associated with immunosuppression and is a frequent second primary among cancer patients. The recent outbreak appears to be spreading from New York City, where 55% of the cases have originated. The population at risk (24-40 yr old) falls in age between that typical of American and European patients (60-70 yr) and that of African patients (less than 20 yr). All patients thus far examined have had anti-hepatitis B antibody or hepatitis B surface antigen, as well as anticytomegalovirus antibody titers. Cytomegalovirus has been cultured from tumor tissue in several cases. All patients in the outbreak have so far been immunosuppressed. The immunological defect appears to be progressive and long-lasting. All patients have had a history of sexually transmitted diseases, some with multiple manifestations such as hepatitis, genital herpes, gonorrhea, and condyloma. Mortality has been exceptionally high, with death occurring in a high percentage of patients within 20 mo, subsequent to unsuccessful combination chemotherapy with doxorubicin, bleomycin, Velban, and dacarbazine. Possible etiologic factors contributing to this outbreak and to malignant transformation in general are discussed. (23 Refs)

SELECTED PRECLINICAL STUDIES

21. DEVELOPMENT OF A NEW MELANOMA MODEL IN C57BL/6 MICE.

Berkelhammer J, Oxenhandler RW, Hook RR, Hennessy JM

Sinclair Comparative Medicine Res. Farm, Univ. Missouri, Route 3, Columbia, MO, 65201

Cancer Res; 42(8):3157-3163 1982

In the present study, we induced melanomas in C57BL/6 mice by a single application of 7,12-dimethylbenz(a)anthracene to the scapular region of 4-day-old mice, followed by twice-weekly applications of croton oil. Of 20 mice treated, melanomas arose in 2 female littermates. The first melanoma (JB/MS) arose 16 wk after initiation of treatment, and the second melanoma (JB/RH) arose 23 wk later. The melanomas maintained their melanotic appearance after sc transplantation to normal C57BL/6 mice and metastasized spontaneously in the transplant recipients. To our knowledge, these are the first melanomas to have been induced in C57BL/6 mice since the B16 melanoma arose spontaneously in 1954. We feel that the JB/MS and JB/RH melanomas provide an excellent comparative system for studies done with the B16 melanoma. These melanomas of recent origin will also facilitate the investigation of biological, immunological, and biochemical parameters that influence the growth and metastasis of malignant melanomas. (Author abstract) (15 Refs)

22. PROSTAGLANDIN E AUGMENTS THE EFFECT OF CHEMOTHERAPY ON B-16 MELANOMA IN VIVO.

Hofer D, Dubitsky A, Marti J, Santoro MG, Reilly P, Jaffe BM
(c/o Jaffe) Dept. Surgery, State Univ. New York Downstate Medical Center, Box 40, 450 Clarkson Ave., Brooklyn, NY, 11203
J Surg Res; 32(6):555-562 1982

The effectiveness of six chemotherapeutic agents (adriamycin, dopamine, 5-fluorouracil, nitrogen mustard, thioTEPA, and vincristine) on B-16 melanoma growth in vivo was compared with the effects of 16,16-dimethyl-PGE2-methyl ester, a long-acting synthetic analog of PGE2 (di-M-PGE2) and of chemotherapy plus di-M-PGE2. Although all the drugs were effective in slowing growth (adriamycin, dopamine, and 5-FU) or decreasing tumor size from baseline values (nitrogen mustard, thioTEPA, and vincristine), the addition of di-M-PGE2 augmented the growth inhibitory effects of each. Changes in tumor diameters were associated with similar changes in tumor cell numbers. In addition, the combinations of di-M-PGE2 plus nitrogen mustard and vincristine decreased the plating efficiency in a clonogenic assay to a greater extent than did either di-M-PGE2 or the cytotoxic drugs alone. Finally, this augmentation was not associated with systemic toxicity or changes in leukocyte count. (Author abstract) (16 Refs)

23. IN VITRO GROWTH PROMOTION IN HUMAN MALIGNANT MELANOMA CELLS BY FIBROBLAST GROWTH FACTOR.

Richmond A, Lawson DH, Nixon DW, Stevens JS, Chawla RK
Clinical Res. Facility, Dept. Medicine, Emory Univ. Sch. Medicine, Atlanta, GA, 30322
Cancer Res; 42(8):3175-3180 1982

Bovine pituitary fibroblast growth factor (FGF) stimulates the incorporation of [3H]thymidine into DNA in serum-depleted cultures of some but not other human melanoma cells. The melanotic malignant melanoma cell line MIRW exhibited a 40% increase in [3H]thymidine incorporation into DNA and a 48% increase in cell number in response to 3.73 x 10(-9) M FGF. This same concentration of FGF produced a 22% increase in [3H]thymidine incorporation in the melanotic melanoma cell line Hs0294. However, FGF had no effect on the amelanotic melanoma cell line Hs0675, early-passage cultures of a human amelanotic melanoma (W-1), or early-passage cultures of a congenital nevus (N-1). (Author abstract) (39 Refs)

24. IDENTIFICATION OF TRANSFORMED GLUCOCORTICOID RECEPTOR FROM DEXAMETHASONE RESISTANT MELANOMA.

Hutchens TW, Hawkins EF, Markland FS
(c/o Hawkins) USC Cancer Center, Research Building One, Room 490, 1720 Zonal Ave., Los Angeles, CA, 90033
J Steroid Biochem; 16(6):705-711 1982

Transformation of the glucocorticoid receptor in RPMI 3460, clone 5 and clone 6 melanoma cells and tumors was examined using a selected chromatographic technique under various experimental conditions. Cytosolic glucocorticoid-receptor complexes from both dexamethasone-sensitive and -resistant melanoma appeared similar to previously activated glucocorticoid receptors from rat liver and kidney in being heterogeneous with respect to chromatographic properties on DEAE-cellulose. Results showed that resistance to dexamethasone-induced changes in growth observed in resistant clone 5 cells and solid tumors cannot be attributed to an inability of the receptor they contain to exist as a stable, transformed complex. (22 Refs)

25. EXPRESSION OF ADHESION-RELATED MEMBRANE COMPONENTS IN ADHERENT VERSUS NONADHERENT HAMSTER MELANOMA CELLS.

Knudsen KA, Damsky CH, Buck CA
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104
J Cell Biochem; 18(2):157-167 1982

Nonadherent variant of hamster melanoma cell line RPMI 3460 was analyzed and its involvement in cell-substratum adhesion investigated. Two variants of RPMI 3460 were used: adherent line CM1 (cell monolayer) and nonadherent line CS1 (cell suspension). CM1 cells could be reversibly rounded and detached from the substratum with either of two antisera raised against material from hamster fibroblasts. Extracellular matrix-associated components did not induce the nonadherent cells to adhere to, or to spread on the substratum. However, continuous exposure to 2 x 1-(-6) M 5-bromodeoxyuridine (BudR) in dark induced a proportion of the cells to adhere to, and to spread on the substratum. Results showed that 10-fold more nonadherent cells than adherent cells were required to remove 50% of the rounding activity from anti-GP serum. NP40 detergent extract of the adherent cells contained approx 14x more total blocking activity than the extract from nonadherent cells. On the other hand, the NP40 extract of cells induced to adhere with BudR expressed similar blocking activity to that extracted from the normally adherent cells. Samples from adherent and BudR-treated cells contained, respectively, 5.5 and 16x more blocking activity than the sample from nonadherent cells. The presence of both blocking activity and the adherent phenotype correlated best with the presence of glycoproteins in the mol wt region of 120,000-140,000. (19 Refs)

26. IN VITRO CHARACTERISTICS OF UVEAL MALIGNANT MELANOMAS.

Felberg NT, Mione T, Shields JA, Federman JL
Wills Eye Hosp., Ninth and Walnut St., Philadelphia, PA, 19107
Arch Ophthalmol; 100(6):987-990 1982

During a 17-mo period, 33 histologically proved posterior uveal melanomas were prepared for in vitro cultivation in our laboratory. Nine of these remained in culture from 5 to 12 passages. Four tumors histologically classified as heavily pigmented spindle B cell type remained as pigmented spindle cell tumors in primary culture. During subcultivation one culture lost pigmentation and exhibited mixed cells. Three other tumors, classified histologically as lightly pigmented spindle B cell type, appeared as amelanotic mixed cells in primary culture and grew as epithelioid cells during subcultivation. Two tumors classified as mixed cell type grew as spindle cells in primary culture. One of these last cultures reverted to mixed cell type on subcultivation. One cell culture has shown pigmentary and morphologic changes with variations in carbon dioxide level and media composition. (Author abstract) (14 Refs)

27. HYPERSENSITIVITY OF ATAXIA TELANGIECTASIA SKIN FIBROBLASTS TO DNA ALKYLATING AGENTS.

Barfknecht TR, Little JB
Chemistry and Life Science Group, Res. Triangle Inst., Post Office Box 12194, Research Triangle Park, NC, 27709
Mutat Res; 94(2):369-382 1982

Three ataxia telangiectasia (AT) skin fibroblasts cells strains, AT4BI, AT5BI, and AT2BE (CRL 1343) were studied for survival following treatment with methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and 4-nitroquinoline-1-oxide (4NQO) and results were compared to those obtained from three normal human fibroblast cell strains. None of the AT fibroblast strains were significantly more sensitive to MNNG treatment than the av normal survival. Similarly, no significant difference was observed in D10 values among the AT fibroblast strains and the normal av D10 value. Strain AT5BI appeared to be moderately sensitive to MMS treatment compared to the normal av survival. Comparison of the D0 value for strain AT5BI, 0.29 milliM (mM) vs the normal av of 0.38 +- 0.03 mM indicated a significant difference in the slope of the survival curve between strain AT5BI and the normal av survival curve. Strain AT4BI was hypersensitive to MMS treatment only when D0S were compared. All three fibroblast strains were significantly more sensitive to treatment with EMS than the normal controls. AT4BI, AT5BI, and AT2BE had D10S of 16, 13, and 15 mM, respectively, vs the normal human fibroblast av D10 value of 28 mM. AT4BI and AT2BE were abnormally sensitive to treatment with 4NQO as compared to the survival of the normal human fibroblast strains. (61 Refs)

28. PHORBOL DIESTER AND EPIDERMAL GROWTH FACTOR RECEPTORS IN 12-O-TETRADECANOYLPHORBOL-13-ACETATE-RESISTANT AND -SENSITIVE MOUSE EPIDERMAL CELLS.

Colburn NH, Gindhart TD, Hegamyer GA, Blumberg PM, Delclos KB, Magun BE, Lockyer J
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Cancer Res; 42(8):3093-3097 1982

Several cell variants have been isolated from promotable mouse JB6 epidermal cells which are resistant either to mitogenic stimulation at quiescence or to promotion of anchorage independence by 12-O-tetradecanoylphorbol-13-acetate (TPA). Such resistant variants would be expected to lack one or more steps in the TPA response pathway leading to mitogenesis or promotion of tumor cell phenotype. This report is concerned with determining whether resistance is attributable to lack of receptors for phorbol diesters or epidermal growth factor (EGF, a potential mediator) or to absence of receptor down modulation following ligand binding. The results show that neither lack of phorbol diester receptors nor absence of down modulation can be demonstrated in the TPA-resistant variants. The phorbol ester binding affinity is also not altered in the resistant variants. The presence of EGF receptors cannot be an absolute requirement for TPA promotion sensitivity since three of the TPA-promotable cell lines lack available EGF receptors. Lack of EGF receptors may account for TPA mitogen resistance in at least three of four resistant variants. The TPA-induced EGF binding decrease occurs in both sensitive and resistant variants. Thus, phorbol diester binding and receptor down modulation remain as possible required events in mitogenic and promotion responses to TPA. EGF receptors are clearly not necessary for TPA promotion of anchorage independence in JB6 cells but may mediate mitogenic stimulation of these cells by TPA. (Author abstract) (31 Refs)

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JAMES K. SELKIRK Oak Ridge National Laboratories	*Metabolic Activation and Macromolecular Binding of Chemical Carcinogens*	#VK02 51 min.
PHILIP C. HANAWALT Stanford University	*Cellular Responses to Damaged DNA*	#VK03 54 min.
CHARLES HEIDELBERGER University of Southern California	*Mutagenesis and Oncogenic Transformation of Mouse Embryo Cells*	#VK04 54 min.
FRED RAPP Milton S. Hershey Medical Center	*The Interaction of Herpesviruses and Host Cells Leading to Latency or Transformation*	#VK05 52 min.
	Panel Discussion	#VK06 31 min.

MECHANISMS OF METASTASIS

ISAIAH FIDLER Frederick Cancer Research Center	*The Heterogeneous Nature of Cancer Metastasis and Implications for Therapy*	#VB01 47 min.
GEORGE POSTE Smith, Kline and French Laboratories	*Phenotypic Analysis of Metastatic Cell Populations*	#VB02 42 min.
LANCE LIOTTA National Cancer Institute	*Tumor Cell Invasion of Basement Membranes and Extracellular Matrices*	#VB03 33 min.
EVERETT SUGARBAKER Miami Cancer Institute	*Some Clinical Characteristics of Metastasis in Man*	#VB04 41 min.

AUTOMATED CYTOLOGY

Part One: Principles and Techniques	#VB05 56 min.
Part Two: Biological Applications	#VB06 52 min.

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MELANOMA AND OTHER SKIN CANCER

Diagnosis, Treatment

SERIES CT22 No. 82/12 DECEMBER, 1982

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DIAGNOSIS

1. PRIMARY MELANOMA THICKNESS CORRELATED WITH REGIONAL LYMPH NODE METASTASES.

Roses DF, Harris MN, Hidalgo D, Valensi QJ, Dubin N

New York Univ. Medical Center, 530 First Ave., New York, NY, 10016

Arch Surg 117(7):921-923 1982

We studied 119 patients with Stage I primary cutaneous malignant melanoma, who were undergoing regional lymph node dissection, to determine the relationship of lymph node metastases to thickness of the primary lesion. The lymph nodes in the dissection specimen were each evaluated by serial sections. None of the patients with lesions less than 1.0 mm thick had nodal micrometastases. When lesions exceeded 1.0 mm in thickness, there was no appreciable increase in the incidence of nodal metastases until a thickness greater than 4.0 mm was reached, in which cases the incidence of metastases was 50%. Predictive variables were determined by multiple logistic regression analysis. Only lesions that were at least 4.0 mm thick and were not located on the upper extremities were significant predictors of lymph node metastases; within this category there

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was a 64% incidence of lymph node metastases. (Author abstract) (14 Refs)

2. HYPOPIGMENTED MYCOSIS FUNGOIDES: REPORT OF FIVE CASES WITH ULTRASTRUCTURAL OBSERVATIONS.

Breathnach SM, McKee PH, Smith NP
(c/o Smith) Skin Tumour Unit, St. John's Hosp., Lisle St., London WC2H 7BJ, England
Br J Dermatol; 106(6):643-649 1982

Five dark-skinned individuals presented with widespread well-demarcated hypopigmented lesions, biopsy of which revealed the histopathological features of mycosis fungoides. Ultrastructural studies showed focal invasion of the epidermis by mycosis cells with degenerative changes in adjacent melanocytes and keratinocytes. The majority of melanocytes exhibited swelling of cytoplasmic organelles and disordered melanogenesis with production of spherical incompletely melanized melanosomes. In addition disintegrating melanocytes were occasionally seen. Perifollicular repigmentation within hypopigmented areas occurred in two patients following clearing of the epidermal infiltrate with PUVA therapy. Mycosis fungoides may present with areas of cutaneous hypopigmentation. (Author abstract) (17 Refs)

3. DEMONSTRATION OF HISTIOCYTES IN THE EPIDERMAL INFILTRATE OF MYCOSIS FUNGOIDES.

Kerdel FA, Morgan EW, MacDonald DM
(c/o MacDonald) Lab. Applied Dermatopathology, Guy's Hosp., London SE1, England
Br J Dermatol; 106(6):651-656 1982

The presence of histiocytes in the epidermal and dermal infiltrate of mycosis fungoides was observed histochemically by revealing a diffuse pattern of acid alpha-naphthyl acetate esterase (ANAE) activity in the cytoplasm, and immunohistochemically by demonstrating the presence of histiocyte-specific 'enzymes', lysozyme, alpha-I-antitrypsin and alpha-I-antichymotrypsin. Histiocytes in the infiltrate of mycosis fungoides may be involved in antigen processing and interaction with T lymphocytes. (Author abstract) (36 Refs)

4. VISUALIZATION OF SKELETAL MUSCLE INVOLVEMENT OF MYCOSIS FUNGOIDES ON 67GA SCINTIGRAPHY.

Shigeno C, Morita R, Fukunaga M, Tsuchiya K, Hino M, Harioka T, Torizuka K
Dept. Nuclear Medicine, Kytoto Univ. Sch. Medicine, 54 Shogoin-kawara-machi, Kyoto 606, Japan
Eur J Nucl Med; 7(7):333-335 1982

An uncommon involvement of the skeletal muscle by mycosis fungoides detected by 67Ga-citrate scintigraphy in a 84-yr-old female is described. The patient developed generalized erythema 17 yr prior to the admission. The patient was successfully treated with corticosteroids and regional radiotherapy. For the following 15 yr the patient's condition had remained good until 2 mo prior to the admission. Diagnosis of mycosis fungoides was made by skin biopsy. The patient was treated with systemic chemotherapy and with regional radiotherapy. The patient's condition progressively deteriorated. The patient died of bronchopneumonia approx 6 wk after 67Ga scanning. Autopsy section from the left leg showed diffuse infiltration of malignant lymphomatous cells in all soft tissue components from the skin to the underlying calf muscle. (11 Refs)

CLINICAL IMMUNOLOGY AND IMMUNOTHERAPY

5. EFFECTS OF DIPHENYLHYDANTOIN ON KILLER CELL ACTIVITY AND OTHER IMMUNOLOGICAL FUNCTIONS. A SEQUENTIAL STUDY INCLUDING THE INTERACTION OF CORYNEBACTERIUM PARVUM IN MELANOMA PATIENTS.

Thatcher N, Wan HH, Swindell R, Wilkinson PM, Crowther D
Dept. Medical Oncology, Christie Hosp. and Holt Radium Inst., Wilmslow Road, Manchester M20 9BX, England
Int J Immunopharmacol; 4(3):167-174 1982

The effects of a single dose of phenytoin (PHEN; 300 mg/square meter) upon killer cell (NK) cytotoxicity, serum immunoglobulins, and T and B cell proportions was investigated prospectively in 11 patients (6 males, 5 females) with metastatic malignant melanoma. No acute change in T lymphocyte rosettes, serum immunoglobulins, and DNA synthesis of lymphocyte cultures were observed after PHEN treatment. An early immunosuppression occurred within 10 hr after PHEN with reductions in lymphocyte count and NK activity. This suppression was reversible, with apparent recovery by 58 hr. Such a feature could explain the transient lymphadenopathy observed before cessation of PHEN medication. The profound and early immunosuppression associated with the first PHEN dose was abrogated by Corynebacterium parvum immunization (iv infusion 2 mg/square meter in 300 ml physiological saline over 3 hr) preceding a second dose of PHEN. While the second dose of PHEN caused some immunosuppression, no increase in T cells, NK, and phytohemagglutinin induced cytotoxicity above initial values was observed. (23 Refs)

6. ACQUIRED IMMUNODEFICIENCY AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Geerling J
Afdeling Inwendige Ziekten, Slotervaartziekenhuis, Amsterdam, The Netherlands
Ned Tijdschr Geneeskd; 126(14):631-633 1982

Recent studies on the sudden increase in the incidence of Kaposi's sarcoma mostly in homosexual men abusing drugs are reviewed. The new syndrome is characterized by very poor prognosis and high incidence of infectious disease indicative of impaired cell-mediated immunity. Kaposi's sarcoma is believed to be of viral etiology. Human leukocyte antigen Dr 5 was found in 10/12 patients examined, while the frequency of this antigen is only 12% in the general population. (7 Refs) (In DUT)

7. PHENOTYPE OF CELLS INVOLVED IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME (BLOOD AND SKIN LESIONS): IMMUNOMORPHOLOGICAL STUDY WITH MONOCLONAL ANTIBODIES.

Schmitt D, Souteyrand P, Brochier J, Czernielewski J, Thivolet J
Dept. Dermatology, Hopital Edouard-Herriot, F-69374 Lyon Cedex 2, France
Acta Derm Venereol (Stockh); 62(3):193-199 1982

The phenotypic expression of immunocompetent cells involved in lesions of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) was studied by using monoclonal antibodies specific for T-cell subsets and HLA-DR antigens (OKT3, T4, T6, T8) (BL 6, BL 5, BL 2). In Sezary syndrome, the phenotype of Sezary cell is homogeneous (T3+, T4+, T8-

, T6-, BL2-) and corresponds to the phenotype expressed by the normal helper T-cell population. At the ultrastructural level, the discontinuous distribution of OKT4 and OKT3 antigenic sites on the cell surface is similar to the HTLA antigens. In skin lesions, the Langerhans cells expressed two specificities shared by normal thymocytes (T6 and BL6). We suggest that the expression of these antigens could be related to the epithelial microenvironment (epithelium-dependent differentiation antigens). The tumoral lymphoid cells infiltrating the skin showed the same phenotype (helper type) as the circulating Sezary cells (T3+, T4+, T8-, T6-). Moreover, The T3+ cells also expressed HLA-DR antigens and corresponded to activated T lymphocytes. The various subpopulations of immunocompetent cells seemed to be related to the MHC-derived antigens. (Author abstract) (29 Refs)

CHEMOTHERAPY

8. DACARBAZINE IN MALIGNANT MELANOMA. RARE, SEVERE SIDE-EFFECT: BUDD-CHIARI SYNDROME.

Doering C, Pickartz H, Orfanos CE, Altenahr E

Universitats-Hautklinik und Poliklinik, Klinikum Steglitz, Freie Universitat Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany

Z Hautkr; 57(13):971-974,976-980 1982

Budd-Chiari syndrome (BCS) was observed in a 54-yr-old man who was receiving dacarbazine (DTIC) as treatment for malignant melanoma. A review of other similar reports is presented. The melanoma was removed from patient's abdomen with a 5 cm margin of healthy tissue. No evidence of metastasis was found. Combination therapy with DTIC (250 mg/square meter of body surface area, administered iv on 5 successive days) and BCG (0.01 ml intracutaneously) was begun 12 days after surgery. On day 5 of DTIC-BCG therapy the patient developed fever, myalgia, and nausea. After treatment with antibiotics the patient improved and was released after 13 days. After injection two of cycle two of DTIC-BCG, because of fever and a drop in blood pressure hospitalization in an intensive-care unit was required. No hepatomegaly was found; cavography, splenoportography, and hepatic venography showed no evidence of obstruction of the hepatic vein. The patient died of renal and hepatic failure after 10 days. Pathological examination indicated BCS. Similar fatal complications involving DTIC therapy had been reported in six other patients, including five with malignant melanoma. Three of these casses had been diagnosed as BCS and three as veno-occlusive disease. DTIC should not be given to patients with a history of liver disease. Patients receiving DTIC should be carefully monitored. When symptoms of liver disease appear, high-dose corticosteroid therapy with fibrinolytic measures should be administered immediately. (40 Refs) (In GER)

RADIOTHERAPY

9. MEGAVOLTAGE ELECTRON BEAM THERAPY IN THE TREATMENT OF BASAL AND SQUAMOUS CELL CARCINOMATA OF THE PINNA.

Hunter RD, Pereira DT, Pointon RC

Christie Hosp. and Holt Radium Inst., Manchester, England

Clin Radiol; 33(3):341-345 1982

Kilovoltage x-ray therapy has considerable limitations when trying to obtain good functional results in patients with skin carcinomas arising on the pinna. Megavoltage electron beams with their better quality of radiation and homogeneous dose distribution have been recognized to have theoretical advantages. Forty-three patients with basal and squamous cell carcinomata arising on the pinna were treated radically using a 10 MeV electron beam. The technique and dosage are described and discussed. Primary cancer control with retention of the pinna was achieved in 34 patients. Salvage pinnectomy was performed in four patients for recurrence and one patient for radiation necrosis. Two patients with large primary tumors failed to resolve and died of their disease. The advantages for the patient of the policy of primary radical electron mean therapy are discussed. (Author abstract) (7 Refs)

MULTIMODAL THERAPY

10. COMBINATION HYPERTHERMIA AND RADIATION THERAPY FOR MALIGNANT MELANOMA.

Kim JH, Hahn EW, Ahmed SA

Dept. Radiation Therapy, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Cancer; 50(3):478-482 1982

Since 1975, clinical studies have been carried out to determine whether radiation when combined with localized hyperthermia evokes improved tumor control compared to that achieved with radiation alone. Local tumor hyperthermia was achieved using radiofrequency inductive heating at 27.12 MHz. In bulky lesions (greater than 100 cm3), radiofrequency conductive heating at 13.56 MHz was also used. More than 100 lesions in 38 patients were treated with radiation alone and hyperthermia in combination with radiation. Most lesions were treated either twice a wk or once a wk, depending on radiation dose fractionation scheme used. The overall result of tumor control rate of the combined therapy is superior to radiation therapy alone (75% vs 46%; p less than 0.01). No enhanced normal tissue morbidity was seen following the combined therapy. The detailed analysis of the treatment results shows that the tumor control rate is dependent on dose per fraction, the total dose, and the initial tumor volume. The radiation alone, at high doses per fraction, was effective in controling 80% of the lesions, if the tumor volume was less than 10 cm3, compared to 30% when the tumor volumes were larger. The combination therapy, on the other hand, effected 80% local tumor control regardless of the tumor volume. The importance of good thermal distribution within the tumor volume, selective heating of the tumor tissues and the sequence and time interval between the combined therapy is discussed. (Author abstract) (20 Refs)

CASE REPORTS

11. SOLITARY SUBCUTANEOUS NODULE AS A PRESENTING SYMPTOM OF PRIMARY MALIGNANT MELANOMA.

Sarig A, Ben-Bassat M, Kaplan I

Dept. Plastic and Maxillofacial Surgery, Beilinson Medical Center, Tel Aviv Univ., Tel Aviv, Israel

Harefuah; 102(5):198-199 1982

A solitary sc nodule of the chest wall was surgically excised from a 39-yr-old man. The lesion was initially diagnosed as metastatic malignant melanoma; the origin of the metastasis could not be determined. At 1-yr follow-up, no recurrence had been observed. The incidence of a solitary sc nodule as the presenting symptom of malignant melanoma is discussed. (9 Refs) (In HEB)

12. PRIMARY KAPOSI'S SARCOMA AND HODGKIN'S DISEASE IN THE SAME LYMPH NODE.

Massarelli G, Tanda F, Denti S

Inst. Morbid Anatomy, Univ. Sassari, Via Matteotti 58, I-07100 Sassari, Italy

Am J Clin Pathol; 78(1):107-111 1982

The occurrence of primary Kaposi's sarcoma in a lymph node affected by Hodgkin's disease is reported. The case concerns a 43-year-old woman with a recurrence of Hodgkin's disease 13 years after its initial diagnosis. In one of four excised supraclavicular nodes a Kaposi's sarcoma was unexpectedly found. The present observation stresses once more that the two diseases are closely related and possibly share the same pathogenesis. (Author abstract) (35 Refs)

SELECTED REPORTS ON ETIOLOGY AND EPIDEMIOLOGY

13. CYTOMEGALOVIRUS AND KAPOSI'S SARCOMA IN YOUNG HOMOSEXUAL MEN.

Drew WL, Miner RC, Ziegler JL, Gullett JH, Abrams DI, Conant MA, Huang ES, Groundwater JR, Volberding P, Mintz L

Dept. Pathology and Lab. Medicine, Mount Zion Hosp. and Medical Center, P.O. Box 7921, San Francisco, CA, 94120

Lancet; 2(8290):125-127 1982

Ten homosexual men with Kaposi's sarcoma (KS) were studied for evidence of cytomegalovirus (CMV) infection. IgG and IgM antibodies to CMV were detected in nine out of nine and in seven out of nine of these patients, respectively. CMV was recovered from body secretions or peripheral blood of seven patients. Viral cultures of KS tumor biopsy specimens were negative in eight out of eight patients, but CMV RNA was detected by in-situ hybridization in two out of three and CMV antigen(s) by immunofluorescence in six out of nine. Normal tissue specimens from three KS patients were negative for CMV antigen. These observations suggest an association of CMV with KS. (Author abstract) (25 Refs)

SELECTED PRECLINICAL STUDIES

14. DEFECTIVE DNA ENDONUCLEASE ACTIVITY ON ANTHRAMYCIN TREATED DNA IN XERODERMA PIGMENTOSUM AND MOUSE MELANOMA CELLS.

Lee DE, Okorodudu AO, Lambert WC, Lambert MW

Dept. Pathology, New Jersey Medical Sch., Newark, NJ, 07103

Biochem Biophys Res Commun; 107(1):395-402 1982

The endonucleolytic activities of nine nonhistone chromosomal proteins isolated from xeroderma pigmentosum (complementation group A) cells (XPA) and their normal counterparts, and from lymphoblastoid and Cloudman mouse melanoma cells, were assayed using anthramycin (AM)-treated circular duplex PM2 DNA. The binding of AM to DNA was determined spectrophotometrically. A DNA enodnuclease activity which was markedly increased against AM-treated DNA in the nonhistone chromatin protein of normal cells was absent from the nuclei of both XPA lymphoblastoid and Cloudman mouse melanoma cells. These results indicated the presence of an endonuclease with marked specificity for AM-DNA in normal human chromatin that is inactive in these other cell types. Other recent results have indicated that in XPA lymphoblastoid cells and mouse melanoma cells, this same chromatin-associated enzyme fraction has markedly increased activity against untreated, linear, duplex DNA. Thus, there may be more than one abnormality in this enzyme activity. (38 Refs)

15. IDENTIFICATION OF AN ONCOFETAL ANTIGEN (GP90) ON MURINE B16 MELANOMA CELLS.

Nishio C, Ishii Y, Ishii K, Kikuchi K

(c/o Ishii) Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan

Eur J Cancer Clin Oncol; 18(6):579-588 1982

A xenoantiserum to murine B16 melanoma cells was developed by immunizing rabbits with cultured B16 melanoma cells. This antiserum could, after extensive absorption with normal C57BL/6 mouse tissues, react with syngeneic (B16) and allogeneic (HP) melanomas as well as with other murine neoplasms, including syngeneic 75S adenocarcinoma, allogeneic myeloma and leukemic T cell lines. The antiserum also cross-reacted with syngeneic fetal fibroblasts and with an allogeneic fetal fibroblast cell line (SC-1) either uninfected or infected with murine leukemia virus (MuLV). Immunoprecipitated material from B16 melanoma cell-surface glycoproteins that had been labeled with [125I] by lactoperoxidase and purified by a Lentil lectin column was analyzed by one-dimensional SDS- and two-dimensional polyacrylamide gel electrophoresis, which disclosed an acidic glycoprotein with a molecular weight (mol wt) of 90 K daltons. Absorption studies suggested that the 90 K mol wt glycoprotein represented the oncofetal moiety expressed in murine melanoma, carcinoma and fetal tissues. When the amount of this antigen in developing C57BL/6 mouse fetuses was measured by absorption assays, we found that it was expressed strongly in those fetuses just before birth. Binding and absorption studies demonstrated that the 90 K mol wt glycoprotein, while being expressed on a variety of fetal and neoplastic cells in mice, did not exist at detectable levels in normal tissues of adult C57BL/6 mice, including tissues of the thymus, lymph node, spleen, liver, brain, lung and kidney. (Author abstract) (26 Refs)

16. THEOPHYLLINE AND MELANOCYTE-STIMULATING HORMONE EFFECTS ON GAMMA-GLUTAMYL TRANSPEPTIDASE AND DOPA REACTIONS IN CULTURED MELANOMA CELLS.

Hu F
Oregon Regional Primate Res. Center, 505 N.W. 185th Ave., Beaverton, OR, 97006

J Invest Dermatol; 79(1):57-62 1982

Gamma-glutamyl transpeptidase (GGT), an enzyme of the gamma-glutamyl cycle, was demonstrated in three of six cell lines derived from a single B16 murine melanoma. Its activity in these cells varied a great deal, appeared to be correlated with the developmental cycle of the cells, and was greatest in young, actively melanogenic cells. Generally, the activity seemed parallel to that of tyrosinase, an enzyme specific for melanin synthesis. The levels of both enzymes tended to decline with prolonged in vitro cultivation, but could be readily renewed after one animal passage. The three cell lines that were GGT-negative were nonpigmented and DOPA-negative; so was a nonmelanogenic and nonmelanocytic rhesus cell line. Melanocyte-stimulating hormone (MSH) and theophylline both enhanced pigmentation in murine melanoma cells. The mechanisms of their action apparently differed. We found that theophylline increased both DOPA- and GGT-reactive cells, whereas MSH only increased DOPA-reactive cells. All three GGT-positive lines were tumorigenic, and two GGT-negative lines were not tumorigenic. Our observations suggest that GGT plays a role in the melanin biosynthetic pathway and that its activity is greater in melanoma cells that are tumorigenic. (Author abstract) (23 Refs)

17. ABNORMAL SENSITIVITY TO UV-RADIATION IN CULTURED SKIN FIBROBLASTS FROM PATIENTS WITH HEREDITARY CUTANEOUS MALIGNANT MELANOMA AND DYSPLASTIC NEVUS SYNDROME.

Smith PJ, Greene MH, Devlin DA, McKeen EA, Paterson MC
MRC Clinical Oncology Radiotherapeutic Unit, The Medical School, Hills Road, Cambridge CB2 2QH, England

Int J Cancer; 30(1):39-45 1982

The dysplastic nevus syndrome (DNS) is a preneoplastic melanocyte abnormality which occurs in families affected by hereditary cutaneous malignant melanoma (HCMM). Although environmental exposures, especially solar UV-irradiation, have been implicated as risk factors in sporadic melanoma, the role of such exposures in the pathogenesis of HCMM is unknown. We have studied the in vitro radiation responses of six nontumor skin fibroblast strains from HCMM/DNS patients representing five families. All six HCMM/DNS strains were found to show some degree of enhanced cell killing sensitivity, compared with normal controls, following 254 nm UV-irradiation. The abnormal survival responses appeared to relate to specific characteristics of HCMM/DNS cells since the six strains had essentially normal sensitivity to gamma-radiation. The enhanced photosensitivity was not associated with abnormal patterns in either DNA repair synthesis or UV-induced inhibition and recovery of de novo DNA synthesis. The survival results are consistent with the hypothesis that the genetically determined predisposition to malignant melanoma may directly or indirectly be the consequence of increased susceptibility to UV-induced cellular damage. (Author abstract) (38 Refs)

18. ANIMAL MODEL OF HUMAN DISEASE. MELANOMA: SINCLAIR SWINE MELANOMA.

Hook RR, Berkelhammer J, Oxenhandler RW
Dept. Microbiology, Sch. Medicine, Univ. Missouri, Columbia, MO

Am J Pathol; 108(1):130-133 1982

Biological features of Sinclair swine melanoma (SSM), similiarities to human melanoma (HM), and the usefulness of SSM as a model for study are discussed. The SSM model system includes a variety of pigmentary abnormalities, including cutaneous melanomas. SSM is manifested by two types of lesions: flat, darkly pigmented lesions composed of cytologically malignant cells, and raised black lesions characteristic of invasive malignant melanoma (MM) with an adjacent intradermal component, analogous to human superficial spreading melanoma. The incidence of spontaneous cutaneous MM in the swine model is 54% among newborn offspring of parents with melanoma and increases to 85% by age 1 yr. The SSM shows a high rate of spontaneous regression, characterized by a reduction in tumor volume and a change in pigmentation from black to white. Regression is apparently related to an immune response by the host. Similarities to human HM include spontaneous development, a wide variety of benign lesions capable of malignant transformation, histopathological similarities, correspondence of metastatic disease to deeply invasive cutaneous tumors, metastatic patterns, tumor-related immune response, and an apparent genetic component. SSM differs from HM in that SSM does not occur in white swine, is not related to UV exposure, and spontaneously regresses in most swine. SSM is useful for studies of malignant transformation and spontaneous regression of melanomas. Experimental breeding herds of melanoma swine are currently maintained. (9 Refs)

19. RETINOIDS INCREASE TRANSGLUTAMINASE ACTIVITY AND INHIBIT ORNITHINE DECARBOXYLASE ACTIVITY IN CHINESE HAMSTER OVARY CELLS AND IN MELANOMA CELLS STIMULATED TO DIFFERENTIATE.

Scott KF, Meyskens FL, Russell DH
(c/o Russell) Dept. Pharmacology, Univ. Arizona Health Sciences Center, Tucson, AZ, 85724

Proc Natl Acad Sci USA; 79(13):4093-4097 1982

Transglutaminase (TGase; R-glutaminyl-peptide:amine gamma-glutamyltransferase, EC 2.3.2.13) and ornithine decarboxylase (ODCase; L-ornithine carboxy-lyase, EC 4.1.1.17) activities were measured after the addition of retinoid analogs to Chinese hamster ovary (CHO) cells released from quiescence and Cloudman S91 (CCL 53.1) mouse melanoma cells stimulated to differentiate with alpha-melanocyte-stimulating hormone (MSH, melanotropin). In both cell culture lines, we detected a biphasic increase in TGase activity and a single peak of ODCase activity within 7 hr after release or stimulation. Retinoid analogs altered the expression of the initial TGase peak in both CHO and melanoma cells. Retinol increased the activity of TGase 1 hr after release in CHO cells, and the activity remained elevated until hr 4. A broad peak of TGase activity also occurred after the addition of alpha-difluoromethylornithne, an irreversible inhibitor of ODC-ase, and after addition of alpha-difluoromethylornithine plus retinol. In mouse melanoma cells, retinoic acid plus MSH markedly enhanced the activity of the initial TGase peak compared to MSH alone. Retinoic acid alone also increased TGase activity biphasically in these cells without the addition of MSH. These studies suggest that retinoid effects that increase TGase activity may alter the ODCase expression in proliferation and differentiation. (Author abstract) (36 Refs)

20. TOXIC EFFECT OF ULTRAVIOLET LIGHT ON MELANOCYTES: USE OF ANIMAL MODELS IN PIGMENT RESEARCH.

Szabo G, Blog FB, Kornhauser A
Lab. Electron Microscopy, Harvard Sch. Dental Medicine, 188 Longwood Ave., Boston, MA, 02115
JNCI; 69(1):245-250 1982

Quantitative histologic investigations on the effect of UV radiation on mammalian melanocytes have shown similarities in the response to carcinogenic chemicals, UV radiation, and 8-methoxypsoralen combined with UV radiation. With all three regimens the melanocyte number increased in mice, whereas long-wavelength UV radiation alone did not change the numerical distribution of these cells. Although it is too early to say that similarity in response of these agents indicates identity in harmful effects of these agents, great care should be exercised in the application of psoralens to human skin in a combined treatment with UV radiation. (Author abstract) (22 Refs)

21. RESPONSES OF PRENEOPLASTIC EPIDERMAL CELLS TO TUMOR PROMOTERS AND GROWTH FACTORS: USE OF PROMOTER-RESISTANT VARIANTS FOR MECHANISM STUDIES.

Colburn NH, Wendel E, Srinivas L
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
J Cell Biochem; 18(3):261-270 1982

The mechanism of late stage promotion was studied in the JB6 mouse epidermal cell line. Second-stage promoters, including phorbol diesters which act both as first- and second-stage promoters, and mezerein, which acts primarily as a second-stage promoter, showed activity in promotion of transformation in JB6 cells. The second-stage antipromoter retinoic acid inhibited promotion of transformation by 12-O-tetradecanoylphorbol-13-acetate (TPA) but the antiproteases antipain and leupeptin, which inhibit first-stage promotion, did not, even at concentrations greater or equal to those that inhibited promotion of transformation in 10T1/2 cells. Three of four mitogen-resistant lines, R219, R6141, and R23, were promotable to anchorage independence by TPA. Thus, promotion of transformation by TPA in JB6 cells can occur without the release-from-quiescence of mitogenic response to TPA. Cross-resistance to mezerein and epidermal growth factor (EGF) occurred in two TPA promotion-resistant clones of JB6, C130, and C125. C125 and C130 showed moderate to high levels of EGF binding while three promotable lines, R219, R6141, and R23, showed little or no EGF binding. Thus, EGF binding is not a requirement for promotion of transformation in JB6 cells by TPA. The role of TPA-induced changes in the sialic-acid-containing plasma membrane glycolipids was investigated. TPA produced a 10-fold decrease in precursor incorporation into a trisialoganglioside and a 2-fold increase in incorporation into an unidentified ganglioside. These findings suggest that gangliosides may be important in promotion of tumor cell phenotype. A model for the sequence of events necessary for promotion of transformation in JB6 cells is proposed. (32 Refs)

22. HUMAN MODELS FOR IDENTIFICATION OF PHOTOSENSITIZING CHEMICALS.

Kligman AM, Kaidbey KH

Duhring Lab., Dept. Dermatology, Univ. Pennsylvania Sch. Medicine, Medical Education Building, 36th and Hamilton Walk, Philadelphia, PA, 19104

JNCI; 69(1):269-272 1982

The human is an appropriate and sensitive animal for identifying photosensitizing drugs administered either topically or systemically. Topically effective phototoxic agents are quite easily revealed when they are applied to normal or scarified skin which is subsequently exposed to 2 x 10(5) j m-2 of near UV light (UVA, 320-400 nm). Systemically effective phototoxic drugs can be identified by exposing intradermally injected sites to either solar-stimulating or UVA radiation. Drugs that cause photocontact allergy can usually be recognized by irradiating pretreated sites 6x over a 3-wk period with a solar simulator and then challenging the sites with UVA. Existing models, the human model especially, should make it possible to recognize important photosensitizing drugs before they are marketed. (Author abstract) (11 Refs)

REVIEWS

23. CHEMICAL PHOTOTOXICITY IN HUMANS.

Epstein JH

450 Sutter St. 1306, San Francisco, CA, 94108

JNCI; 69(1):265-268 1982

Phototoxic reactions may be induced by endogenous or exogenous chemicals. Endogenous photosensitizers made by the body include porphyrin molecules which are responsible for the photocutaneous syndromes noted in the porphyrias. Exogenous photosensitizers may arrive on the skin through topical applications or may be distributed through the vasculature. Topical photosensitizers are found in cosmetics, medications, plants, and industrial and air pollutant emissions. Systemic photosensitizers consist primarily of therapeutic agents. Acute and chronic phototoxic reactions may occur. The acute response is generally characterized by erythema and edema followed by hyperpigmentation and desquamation. The end point of chronic damage may be cutaneous cancer formation. The mechanisms of these changes may well relate to nucleic acid injury, protein and membrane damage, and alterations in other nuclear and cytoplasmic molecular structures. However, translation of experimental information into human responses remains to be clarified. A great deal of investigation is still needed in developing assays for detecting phototoxic chemicals and for defining mechanisms involved in phototoxic events in human skin. (Author abstract) (38 Refs)

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